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Page	Line	
516	4*	*for* " $C_{12}H_{10}O_2N_4$ " *read* " $C_{13}H_{20}O_2N_4$ ".
517	28*	*for* " $C_{17}H_{14}O_2NCl$" *read* " $C_7H_{14}O_2NCl$ ".
1108	6*	*for* " C, 15·7 " (in two places) *read* " S, 15·7 ".
1115	table	*for* " Benzylamine " *read* " *cyclo*Hexylamine ".
1116	13*	*for* " methano " *read* " methanol ".
1458, 1459		Interchange figs. 1 and 2.
1682	4	*for* " $0{\cdot}00722t^2$ " *read* " $0{\cdot}000722t^2$ ".
1726		*for* " **3:4:5:6-Dibenzyl***cyclo***hepta-1:3:5-triene** " *read* " **3:4:5:6-Dibenz***cyclo***hepta-1:3:5-triene** ".
1726		*for* " **3:4:5:6-Dibenzyl***cyclo***hepta-3:5-diene** " *read* " **3:4:5:6-Dibenz***cyclo***hepta-3:5-diene** ".

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126	6	*for* " 272° " *read* " 227° ".
126	7*	*for* " pyridoacridine " *read* " pyridoacridone ".
—		In the Table of Contents of the June *Journal*, paper 172, *for* " Esters of carbonic acid " *read* " Esters of carbamic acid ".
176		4 of Summary; page 177, lines 15 and 25 of text, *for* " ·CO·[CH:CH]$_n$·CO· " *read* " ·CO·[$\overset{|}{C}$:$\overset{|}{C}$]$_n$·CO· ".
220	6*	*for* " 2:4:5-triaminopyrimidine " *read* " 2:4:5-triamino-6-hydroxypyrimidine ".
223	14*	*for* " 2:4:5-triaminopyrimidine " *read* " 2:4:5-triamino-6-hydroxypyrimidine ".
518	15	*for* " 4-hydroxy-2-methylquinoxaline " *read* " 4-hydroxy-2-methylquinazoline ".
559	last	*for* " at " *read* " of ".
560	6 and in Table heading,	*for* " carbaminoyl " *read* " carbamyl ".
565	19	*for* " 1017 " *read* " 1917 ".
566	4	Before " *citrifolia* " insert " *Morinda* ".
569		In formula (II), the " Me " on the left should be raised so as to be ortho to the " OH ".
710	11	*for* " *op. cit.*, p. 39 " *read* " ' Practical Physiological Chemistry ', Heffer, Cambridge, 5th edition, 1919, p. 39 ".
710	16	*for* " *op. cit.*, p. 80 " *read* " ' Practical Physiological Chemistry ', Heffer, Cambridge, 9th edition, 1933, p. 80 ".
713	8 (of text)	*for* " bibliographic " *read* " biographic ".
878		In formula (X), " R " should be attached to the right-hand " O " by the vertical bond.
—		In the Table of Contents of the July *Journal*, paper 204 (" The Relative Strengths of Some Fatty Acids ") should have been classified under " General, Physical, and Inorganic ", and not under " Organic ". Paper 215 was omitted from the Table of Contents; it should have been included under " Organic ", and " Ives, D. J. G." and " Nettleton, (Miss) M. R." should have been included in the Index of Authors' Names.
Plate facing p. 986.		In Fig. 10, *for* " β " *read* " β' ".
1043	2*	*for* " (V) " *read* " (VI) ".
1052	9	*for* " iodide " *read* " iodine ".
1052	14	*for* " Iodide " *read* " Iodine ".
1182		In the lower formula, (*a*) and (*b*) should be interchanged.
1263	28—29	*for* " (XII; R = H) " *read* " (XII) ".
1508		In Formula (IV), the " Br " should be attached to the " C " immediately below it by a vertical bond.
1596	22*	for " 2-*acetoxyethyl sulphide* " read " *methyl* 2-*acetoxyethyl sulphide* ".
1602	34	*for* " chromate " *read* " chromite ".

* From bottom of main text.

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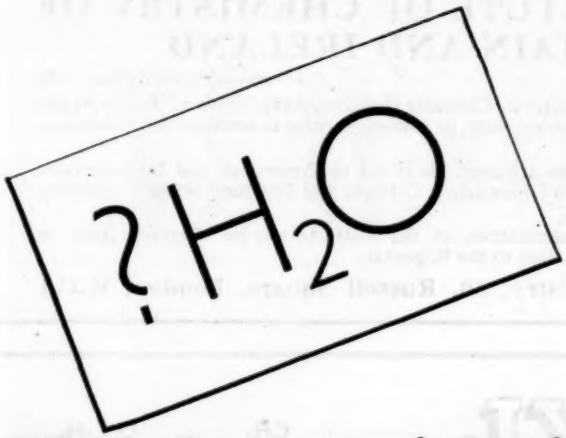

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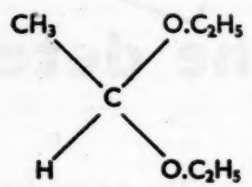

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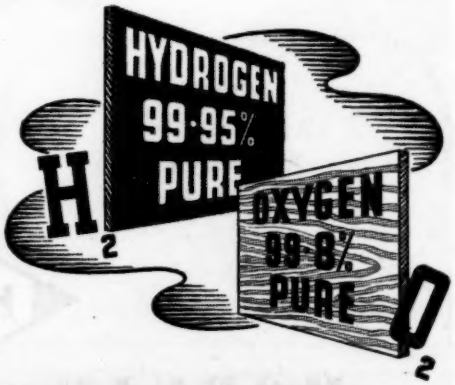

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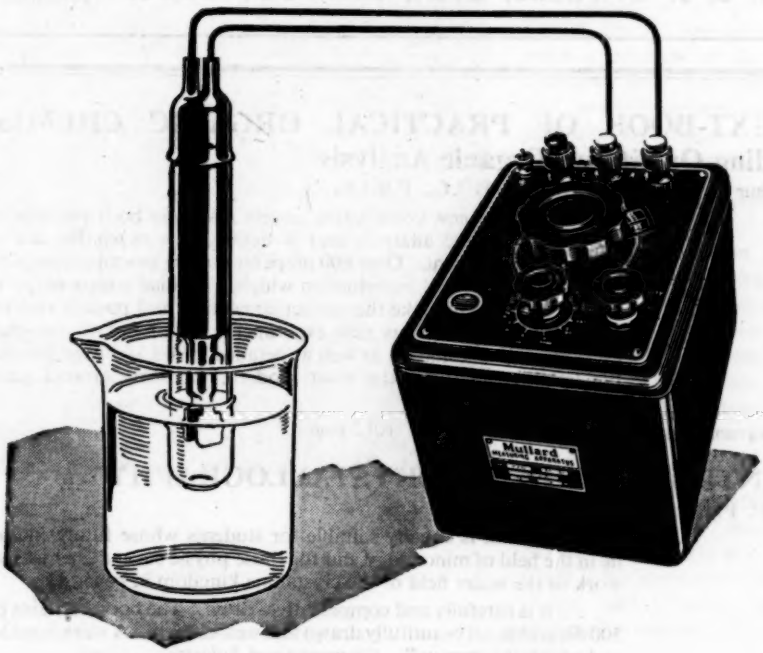

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1. *Rearrangement and Substitution in Anionotropic Systems. Part I. Test for Bimolecular Isomerisation in α-Phenylallyl Esters.*

By A. G. Catchpole and E. D. Hughes.

In these papers a relationship is traced between the mechanism of aliphatic substitution and the mechanism of isomerisation and of substitution, with and without rearrangement, in anionotropic systems. Isomerisation may generally be regarded as a special case of substitution with rearrangement, and it is shown that it usually depends, like the unimolecular mechanism of aliphatic substitution, on an ionisation process (equation 1 below). In the isomerisation of α- to γ-phenylallyl *p*-nitrobenzoate, in methyl cyanide and acetic anhydride as solvents, the rate is increased by added lithium *p*-nitrobenzoate, but the increase is of a type which can be accounted for as an effect of ionic strength on the rate of ionisation to the mesomeric carbon cation. No evidence of any considerable incursion of a bimolecular isomerisation (see equation 2) could be obtained under conditions known from our experience of bimolecular aliphatic substitution to be favourable. Detailed discussion is deferred to Part III (this vol., p. 8).

These papers are the first of a series in which it is intended to carry further forward an investigation which was commenced by Burton and Ingold in 1928 and continued in fairly direct sequence by Meisenheimer and his collaborators until Professor Meisenheimer's death in 1934. Our main reason for taking up the subject in 1937 was that, since a connection between the mechanism of anionotropy and of substitution at a saturated carbon atom was manifest, it was opportune to apply the knowledge gained in the studies of substitution, which had then been partly completed, to a re-investigation, along somewhat analogous lines, of rearrangement and substitution in anionotropic systems. The full presentation of our initial results has been delayed, although a partial summary was published by one of us in 1941 (*Trans. Faraday Soc.*, 1941, **37**, 627).

Burton and Ingold (*J.*, 1928, 904) adduced reasons for the belief that anionotropic change is initiated by the separation of the mobile group as an anion, the simultaneously produced carbonium ion being necessarily mesomeric, and therefore capable of recombining with an anion in either of two alternative positions. Obviously, if the anion with which the carbonium ion recombines is of the same kind as that originally eliminated, an isomeric rearrangement may result:

$$R{-}CHX{-}CH{=}CH_2 \rightleftharpoons \bar{X} + [R{-}CH{-}\overset{\frown}{CH}{-}CH_2]^+ \rightleftharpoons R{-}CH{=}CH{-}CH_2{-}X \quad . \quad (1)$$

However, recombination with another anion derived from some foreign source is equally possible, and this would lead to substitution with or without rearrangement. Therefore, in this mechanism, isomeric rearrangement is to be regarded as a particular case of substitution with rearrangement. Further, the substitution mechanism itself is now seen to be a particular case of the unimolecular substitution mechanism, S_N1, which since 1935 has become recognised as general among aliphatic compounds.

One result of these successive inclusions of the particular within the more general was that the second type of mechanism which has been found to be common in aliphatic substitution, namely, the bimolecular mechanism, S_N2, was hypothetically particularised, in corresponding stages, to yield, for anionotropic systems, first, a possible bimolecular mechanism for substitution with rearrangement, and, secondly, a possible mechanism for isomeric rearrangement (Hughes, *Trans. Faraday Soc.*, 1938, **34**, 185). The latter mechanism may be written

$$R{-}CHX{-}CH{=}CH_2 + \bar{X} \rightleftharpoons \bar{X} + R{-}CH{=}CH{-}CH_2{-}X \quad . \quad . \quad . \quad (2)$$

This idea contained a possible interpretation of some experiments carried out by Burton. He showed (*J.*, 1928, 1650) that the isomerisation of α- to γ-phenylallyl *p*-nitrobenzoate, in

organic dipolar solvents such as phenyl cyanide and acetic anhydride, could be largely diverted into a non-isomeric substitution with rearrangement by the introduction of acetate ions. The production in this experiment of a high proportion of γ-phenylallyl (cinnamyl) acetate in place of *p*-nitrobenzoate was regarded by Burton as strong evidence in favour of the ionisation mechanism of rearrangement. He adduced further support for this conclusion by means of rate comparisons which excluded the alternative idea of successive internal isomerisation and group replacement (*J.*, 1934, 1268).

The possibility remains, however, that the bimolecular mechanism represented in equation (2) above might account for the isomerisation, and, by a completely natural generalisation, for the substitution with rearrangement which occurs on the introduction of acetate ions. As to the isomerisation, no fundamental difficulty need be felt in assuming the availability of *p*-nitrobenzoate ions in small concentration; for Meisenheimer, Schmidt, and Schäfer have shown (*Annalen*, 1933, **501**, 131) that the isomerisation of α-phenylallyl *p*-nitrobenzoate is accompanied by side reactions, which in certain conditions include the formation of *p*-nitrobenzoic acid.

The main verifiable consequence of this hypothesis of the mechanism of anionotropic isomerisation is that the anion corresponding to the mobile group should be a powerful catalyst for the rearrangement. We have sought to apply this test in the example of the isomerisation of α-phenylallyl *p*-nitrobenzoate * by examining the effect of added *p*-nitrobenzoate ions on the rate of the rearrangement. The rate of isomerisation of α-phenylallyl *p*-nitrobenzoate, as well as of α-phenylallyl 3 : 4 : 5-tribromobenzoate, was first investigated by Meisenheimer, Schmidt, and Schäfer (*loc. cit.*) by the method of thermal analysis. Owing to the difficulty of inducing crystallisation in the mixtures obtained, the method is, as they mildly remark, " keineswegs restlos erfreulich "; but they were able, nevertheless, to show that, while autocatalytic phenomena appear when the rearrangements are carried out in the absence of a solvent, the isomerisations of both esters in solution approximately follow the first-order rate law. We used the same method and consider that their description of it would be an understatement if it were applied to our conditions: the difficulties mentioned have, in our hands, precluded anything better than semi-quantitative results, which, however, settled the main point in which we were interested.

We show that, in methyl cyanide and acetic anhydride as solvents, the effect of the addition of lithium *p*-nitrobenzoate, though considerable, is not greater than can be accounted for as an activity effect of an added salt on a reaction whose rate is controlled by an ionic dissociation.

In explanation it may be pointed out that, according to the ionisation mechanism of equation (1), there should be no acceleration by *p*-nitrobenzoate ions under the mass law, the rate being proportional to the concentration of the original ester only. On the other hand, there should be an accelerative activity effect, due essentially to the electrostatic attraction of any pre-existing ions for the ions that can be formed by dissociation of the original ester. This can raise the rate by a small multiple at the concentrations at which it is convenient to work, as was shown, both practically and theoretically, in analogous instances, by Bateman, Church, Hughes, Ingold, and Taher (*J.*, 1940, 979). In an example even more closely related to our present case, namely, the unimolecular solvolysis of α-methylallyl chloride in acetic acid, a considerable ionic strength effect of acetate ions has been clearly demonstrated by Roberts, Young, and Winstein (*J. Amer. Chem. Soc.*, 1942, **64**, 2157). The requirements of the bimolecular mechanism of equation (2) are quite different. Here activity effects are expected to be comparatively negligible in such experiments as ours, and, if observable at all, they should produce a quite small retardation (*idem, ibid.*). On the other hand, the mass law requires a very great acceleration; for the rate is now proportional to [Anion] [Ester], and the anion concentrations (0·1 to 1·1M) of which we investigated the effects were overwhelmingly large in comparison with the traces which might be formed from the esters.

The rate of isomerisation is definitely increased by the addition of lithium *p*-nitrobenzoate. For example, in methyl cyanide as solvent ([α-phenylallyl *p*-nitrobenzoate] ~ 0·35M) the presence of 0·1M ions increased the extent of isomerisation under comparable conditions from about 28% to about 50%. In acetic anhydride solution, a considerable accelerative effect was observed with 1M concentrations of salt (see experimental section), but it should be noted that the rate of isomerisation in the complete absence of extraneous ions was, nevertheless, of a

* This compound is a particularly appropriate example for study, because, apart from the general desirability of applying our tests to a system for which the data of the previous workers were available, there is a special convenience established by their work, namely, that the isomerisation to γ-phenylallyl *p*-nitrobenzoate can be carried substantially to completion in suitable solvents.

comparable order of magnitude to that obtaining even with such high concentrations of lithium *p*-nitrobenzoate. In no case were we able to induce a facile reaction in the presence of added salt when little or no isomerisation existed in its absence.

We may conclude that the bimolecular mechanism of isomerisation plays no rôle of any importance in the isomerisation of α-phenylallyl *p*-nitrobenzoate in the absence of added salt in the solvents used and under the conditions of our experiments. Until we have completed a more refined and extensive investigation (the results of which will be reported later) of this and other structures we cannot, of course, assert that the isomerisation reactions of anionotropic systems generally, and particularly those taking place in the presence of considerable concentrations of extraneous ions of the same kind as the mobile anion from the structure undergoing rearrangement, cannot in any circumstances follow the bimolecular route; but we may at this stage express the view that this type of mechanism is at least uncommon, if not non-existent, in anionotropic systems. Further evidence bearing on this point is given immediately below and in the following paper.

Reference may now be made to some similar experiments by Meisenheimer and Beutter (*Annalen*, 1934, **508**, 58), who used α-phenylallyl acetate and metallic acetates in place of our *p*-nitrobenzoates, and operated in acetic acid medium. Consistently with our results, they found that added lithium and potassium acetates had only fairly small effects on the rate of isomerisation of the ester. Originally we were doubtful whether these results were significant, for the reason that the acid catalysis of anionotropic change is well established, and we had no knowledge of its quantitative importance in Meisenheimer and Beutter's acidic solvent, or of the extent to which it would be modified by the addition of salts, which would suppress the hydrogen-ion concentration. It seemed to us that these authors might have been observing the difference of two contrary effects. Furthermore, since water had not been excluded from the solvent, the results could have been complicated by hydrolysis and subsequent re-esterification. A detailed analysis of Meisenheimer and Beutter's results indicates that these disturbances were, in fact, not completely eliminated, but the absence of any great increase of rate with added acetate ions, taken in conjunction with our similar results in dry, non-acidic solvents, may be regarded as affording some evidence that the bimolecular mechanism is also unimportant in the isomerisation of α-phenylallyl acetate under these conditions. Meisenheimer and Beutter also showed that lithium chloride caused a considerable increase in the rate of isomerisation, although it took no stoicheiometric part in the reaction, and, since this is unlikely to be anything other than an activity effect, its existence affords some confirmation of the adequacy of the activity explanation generally.

The existence of salt effects of the order of magnitude of those which appear in Meisenheimer and Beutter's experiments, and in our own, would be very difficult to reconcile with a purely intramolecular picture of the isomeric changes concerned (cf. also the following papers); and we may remark in conclusion that our investigations point to the existence of ionisation as a mechanism of anionotropic rearrangement, and confirm the work of Burton and Ingold in this field of study.

Experimental.

The esters were prepared as described by Burton and Ingold and by Meisenheimer, Schmidt, and Schäfer (*loc. cit.*). Lithium *p*-nitrobenzoate was obtained from *p*-nitrobenzoic acid by exact neutralisation with lithium hydroxide in methyl alcohol and crystallisation from the same solvent.

The isomerisation experiments were carried out in small sealed bulbs, pairs of tubes each containing fixed quantities of α-phenylallyl *p*-nitrobenzoate and solvent, and one of them an added amount of lithium *p*-nitrobenzoate, being heated at the same temperature for known times, after which they were cooled and opened, and the products examined. Two solvents and a variety of heating periods and temperatures were used. The method of working up the products for examination varied slightly according to the solvent employed, as described later. The m. ps. of the solids obtained were determined in capillary tubes with adequate stirring both of the material and of the bath, and with special attention given to the clearing temperatures. The m. ps. observed, together with m. ps. of mixtures with α- or γ-phenylallyl *p*-nitrobenzoate in so far as these were required in order to identify the isolated mixture with the correct branch of the curve, were used in conjunction with the m. p.–composition curve for known mixtures of the two esters (Meisenheimer, Schmidt, and Schäfer, *loc. cit.*) to estimate the rough composition in each case. We record below the details of some typical experiments in the solvents employed.

Methyl Cyanide.—Pairs of tubes each containing α-phenylallyl *p*-nitrobenzoate (0·5 g.) and methyl cyanide (5 ml.), with addition of lithium *p*-nitrobenzoate (0·1 g.) to one, were heated at 112° for 12 hours. The tubes were then cooled and opened, and the solvent was removed under reduced pressure so that no further isomerisation took place. The mixed esters were then extracted completely with light petroleum. The petroleum solution was filtered and the solvent again removed under reduced pressure; the product solidified on cooling. The solid thus obtained from the isomerisation without the addition of lithium *p*-nitrobenzoate had m. p. 35° (corresponding to about 28% of γ-phenylallyl *p*-nitrobenzoate) and that

obtained from the reaction in the presence of the salt had m. p. 48—54° (corresponding to about 50% of γ-phenylallyl *p*-nitrobenzoate). Results obtained after heating tubes, with contents the same as the above, for 2 hours at 120° indicated that the presence of the salt had increased the isomerisation approximately from 10% to 20%.

Acetic Anhydride.—Preliminary experiments showed that a small amount of impurity was present in the products resulting from the use of this solvent, and the procedure used in the isolation of the esters was modified as follows. The tubes, after being heated, were broken into ice-cold water and the mixture was made just alkaline with dilute sodium hydroxide solution. After much stirring, the oily product then partly solidified. It was dissolved in light petroleum, and the solution was filtered from traces of residue, concentrated to a small volume, and cooled. The bulk of the product crystallised after this treatment and was separated, dried, and examined as previously described. A second (small) fraction was obtained after complete removal of the petroleum solvent, and this solidified with great difficulty after being cooled and agitated. When α-phenylallyl *p*-nitrobenzoate (5 g.) was heated for 20 hours in acetic anhydride (25 ml.) at 100°, the two fractions obtained as described had the following m. ps.: (1) 58—64°, (2) 54° (corresponding to about 60% of γ-phenylallyl *p*-nitrobenzoate). The addition of 5 g. of lithium *p*-nitrobenzoate to a similar solution containing 5 g. of the ester in 25 ml. of solvent gave, after 5 hours' heating at 100° and subsequent treatment as before, two fractions as follows: (1) m. p. 74°, (2) m. p. 62—64°, these results indicating about 85% conversion into γ-phenylallyl *p*-nitrobenzoate in the presence of the salt.

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2. *Rearrangement and Substitution in Anionotropic Systems. Part II. Test for Bimolecular Rearrangement, and Confirmation of the Ionic Mechanism of Rearrangement, from Product Compositions in Substitutions of α- and γ-Methylallyl Halides.*

By A. G. CATCHPOLE and E. D. HUGHES.

In continuation of the investigations outlined in the preceding paper, we show in the example of the etholysis of α- and γ-methylallyl chlorides that, whereas the first-order solvolytic reactions of the chlorides, which are largely unimolecular in mechanism, give rise to a mixture of isomeric ethers of approximately the same composition in both cases, the bimolecular reactions with sodium ethoxide in ethyl alcohol give only the ether of corresponding structure to the chloride used. Thus, while there is evidence for a unimolecular mechanism of replacement, involving the formation of a mesomeric carbon cation (S_N1—see below), and for a direct bimolecular substitution without rearrangement (S_N2), we find no indication of bimolecular replacement with rearrangement (S_N2'). The observations are entirely consistent with our failure to realise a bimolecular mechanism of isomerisation (preceding paper). The full significance of both results is discussed in the following paper.

IN Part I we outlined the application of recent advances in our knowledge of the mechanism of aliphatic substitution to the problems of rearrangement and substitution in anionotropic compounds and discussed in more detail the special case of isomerisation in these systems. We now proceed with a further consideration of the mechanism of anionotropic substitution. Burton and Ingold's mechanism, now regarded as a particular form of the general unimolecular mechanism of nucleophilic substitution, may for this case be formulated as follows:

$$R{-}CHX{-}CH{=}CHR' \longrightarrow \bar{X} + [R{-}CH{\frown}CH{-}CHR']^{+} \xrightarrow{\bar{Y}} \begin{cases} R{-}CHY{-}CH{=}CHR' \\ R{-}CH{=}CH{-}CHYR' \end{cases} \ldots (S_N1)$$

Obviously, this mechanism provides for substitution without or with rearrangement of the anionotropic system. It is undoubtedly operative over a wide range of substances and conditions: the evidence, partly derived from this paper, will be collated in Part III.

The analogous particularisation of the bimolecular mechanism of substitution is represented below; in theory, this scheme also provides for substitution either without rearrangement of the anionotropic system, S_N2, or with such rearrangement, S_N2':

$$\bar{Y} + R{-}CHX{-}CH{=}CHR' \longrightarrow R{-}CHY{-}CH{=}CHR' + \bar{X} \ldots (S_N2)$$

$$R{-}CHX{-}CH{=}CHR' + \bar{Y} \longrightarrow \bar{X} + R{-}CH{=}CH{-}CHYR' \ldots (S_N2')$$

We set ourselves two experimental problems, one relating to each of these two main types of mechanism. The first was to set up conditions of substitution, kinetically consistent with the

unimolecular mechanism, for two isomerides R—CHX—CH=CHR′ and R—CH=CH—CHXR′, and then to ascertain whether each yields an identical mixture of the substitution products R—CHY—CH=CHR′ and R—CH=CH—CHYR′, both the reactants and the products being sufficiently stable not to undergo mutual isomerisation under the experimental conditions employed. An identical mixture should result if the reaction proceeds by way of a carbonium ion which is common to both of the original substances and to both of the products. The second problem was to set up, for each of the two original isomerides, conditions of substitution in which the bimolecular mechanism could kinetically be proved to have taken substantially complete control; and then to ascertain by a similar study of the product composition whether each substitution, besides pursuing the familiar route in which the entering group becomes attached to the carbon atom from which the removed group is expelled (S_N2), also assumes a form in which the entering group becomes attached to the other end of a rearranged anionotropic system (S_N2'). Our failure to establish bimolecular rearrangement in isomerisation lent special interest to the question of the existence of bimolecular rearrangement in the substitution reactions of an anionotropic system.

Desiring a system of simple constitution and limited mobility, we considered the case of α- and γ-methylallyl bromides, our attention having been drawn to these compounds by previous studies of their formation and interconversion and particularly by the work of Young and of Kharasch and their collaborators (Winstein and Young, *J. Amer. Chem. Soc.*, **1936**, **58**, 104; Young and Lane, *ibid.*, **1937**, **59**, **2051**; Kharasch, Margolis, and Mayo, *J. Org. Chem.*, **1936**, **1**, **393**). The corresponding chlorides (Kharasch, Kritchevsky, and Mayo, *J. Org. Chem.*, **1937**, **2**, **489**) are, however, much more easily purified to the extent necessary for the kinetic and product experiments, as well as having a wider margin of stability; consequently, we selected these compounds for our investigations. The substitution studied was their ethyl alcoholysis, both in ethyl alcohol alone and in solutions containing various concentrations of sodium ethoxide.

It is convenient to include the detailed account of the preliminary kinetic experiments in a forthcoming paper, since, in the subsequent course of our work, these experiments have been extended into a kinetic investigation of considerably wider scope (which is not yet quite complete) involving a number of simple and substituted allyl halides other than those with which we are now concerned, as well as a general consideration of medium effects, activation energies, and other matters which are only indirectly connected with the present problem. The main point for our immediate purpose is the determination of the limits of sodium ethoxide concentration above which the kinetic order is substantially second. These limits follow from the measured first- and second-order rate constants for alcoholysis in alcohol solutions containing different concentrations of sodium ethoxide. The alcoholysis of α-methylallyl chloride under the conditions used is a nearly pure second-order reaction in the presence of ethoxide concentrations above about 0·5N. For γ-methylallyl (crotyl) chloride the tendency to second-order substitution is greater, to the extent that the approximate limit may be set about five times lower than that applying to the α-methylallyl compound.

In order to exclude any trace of accompanying unimolecular reactions the experiments on the products formed in bimolecular substitution were carried out in 2·7N-ethyl-alcoholic sodium ethoxide. The first-order solvolytic reactions, on the other hand, were conducted in substantially neutral alcoholic solutions.

It is by now a commonplace that first-order solvolytic substitutions are not proved by their kinetic order alone to be unimolecular, because bimolecular substitutions with the solvent molecule as the substituting agent require the same kinetic order. The latter interpretation is definitely excluded only when we can show, for instance, that the compound substituted is insensitive to substituting agents which are more strongly basic than the solvent molecule. With α- and γ-methylallyl chlorides in dry ethyl alcohol as solvent there is sensitivity to the very strongly basic ethoxide ion, as shown by the results contained in Table I.

TABLE I.

Rates of Alcoholysis of α- and γ-Methylallyl Chlorides.

(Temp. 99·5°. Initial [Halide] ~ 0·05M. k_1 = first-order constant in min.$^{-1}$. k_2 = second-order constant in min.$^{-1}$ g.-mol.$^{-1}$ l.)

	α-Methylallyl chloride.	γ-Methylallyl chloride.
NaOEt = 0 : 10^3k_1	1·76	4·88
NaOEt = 1M : 10^3k_2	91·5	1630

Taking account of the concentration of the solvent for the purpose of an order-of-magnitude calculation, the specific rates which would have to represent the activity of alcohol in assumed bimolecular reactions with α- and γ-methylallyl chlorides are about 10^{-3}—10^{-4} times smaller than the corresponding rates for the reactions with ethoxide ions. In reactions for which other evidence indicates a bimolecular mechanism this rate ratio is of order 10^{-5}—10^{-6} (cf. Bateman, Cooper, Hughes, and Ingold, *J.*, 1940, 925). In the case of α-methylallyl chloride, the sensitivity is such as to suggest a substantially unimolecular mechanism in the complete absence of added ethoxide ions, though it is not sufficiently limited definitely to establish a unimolecular mechanism to the complete exclusion of any bimolecular contribution. A duplex constitution for the reaction between γ-methylallyl chloride and ethyl alcohol is rendered very probable by the results indicated. Nevertheless, since the second-order reactions with sodium ethoxide are indubitably bimolecular, we have two conditions of reaction, corresponding to first- and second-order kinetics, for which product analyses are of interest.

The bimolecular replacement was effected with a saturated solution of sodium ethoxide (2·7N) in ethyl alcohol at the boiling point of the solution. All the usual precautions having been taken with regard to the standardisation and checking of the method of isolation (see experimental section), the ethers formed were isolated and analysed refractometrically. The results are in Table II. They show that each halide gives an ethyl ether of corresponding structure; in other words that, while bimolecular substitution without rearrangement of the anionotropic system (S_N2) freely occurs with both halides, there is no accompanying bimolecular substitution with rearrangement (S_N2').

TABLE II.

Product Composition in Second-order Ethyl Alcoholysis of α- and γ-Methylallyl Chlorides.

Chloride or mixture of chlorides used.	Ethyl γ-methylallyl ether in product (%).
α-Methylallyl chloride	0
γ-Methylallyl chloride	100
Mixture of chlorides { 71% α-methylallyl, 29% γ-methylallyl }	28

For the first-order reactions, the experiments were again carried out at the boiling point of the solution, which was prevented from running acid by adding an indicator and titrating with alcoholic sodium ethoxide during the course of the reaction. The solutions were thus kept as near the neutral point as possible, but, of course, momentary local concentrations of alkali were impossible to avoid, though by rapid agitation they could be minimised. The results, summarised in Table III, show that each of the isomeric chlorides, on alcoholysis under the conditions mentioned, gives a mixture of isomeric ethyl ethers of similar composition. The direction of the differences in composition is such that they may be attributed either to our failure entirely to avoid such momentary local concentration of alkali during the experiments as would lead to a small amount of simultaneous substitution with ethoxide ions, or to a limited concomitant bimolecular reaction with solvent molecules. Doubtless, the incursion of a bimolecular replacement would be more important in the case of γ-methylallyl chloride, as the results of Table I clearly show, and we regard the figures obtained with α-methylallyl chloride as approximating more closely to the probable result of substitution by a unimolecular mechanism.

TABLE III.

Product Composition in First-order Ethyl Alcoholysis of α- and γ-Methylallyl Chlorides.

Chloride or mixture of chlorides used.	Ethyl γ-methylallyl ether in product (%).
α-Methylallyl chloride	82
γ-Methylallyl chloride	92
Mixture of chlorides { 32% α-methylallyl, 68% γ-methylallyl }	92

In the bimolecular reaction, it is evident from the product studies themselves (Table II) that no isomerisation of the halides takes place under the conditions used. For the first-order reaction, on the other hand, the product analysis does not provide a similar check, and it is necessary to discuss the possibility that isomerisation of the halides occurs by some mechanism which does not involve ionisation.* Evidence is available indicating that any considerable

* Isomerisation of the halides through an ionic intermediate would not vitiate our conclusion with regard to the mesomeric nature of the ion, but we think it is unlikely to occur to any considerable extent under the conditions employed.

isomerisation of this type is improbable under the conditions employed in our solvolytic reactions. Briefly, the chief items of evidence are as follows: First, the pure isomers did not undergo any detectable change on being boiled under reflux for several hours, either alone or in solution in an inert solvent such as acetone. Secondly, when the two pure chlorides are dissolved in ethyl alcohol under conditions approximating to those used in our product experiments, the first-order rate constants for the formation of the mixed ethers are different in the two cases (cf. Table I: see also Roberts, Young, and Winstein, *J. Amer. Chem. Soc.*, 1942, **64**, 2157), thus eliminating the possibility that a prior isomerisation may occur in the alcoholic solvent, to give in each case the same equilibrium mixture of chlorides. The absence of isomerisation in the products of reaction (after their formation) under the conditions of our experiments is proved by the results for the bimolecular substitution reactions (Table II); evidently no change occurs when the ethers are boiled under reflux in alcoholic solution. Further evidence on this point was obtained by conducting " recovery " experiments involving known mixtures of the two ethers; no change in composition was detected under the conditions employed for either the first- or the second-order substitution reactions.

After the publication in summary of these results (*Trans. Faraday Soc.*, 1941, **37**, 627) a paper by Roberts, Young, and Winstein appeared (*loc. cit.*) recording the results of an independent investigation which provides excellent confirmation as far as there is overlap. These authors studied the reactions of α- and γ-methylallyl chlorides with both ethoxide ions in ethyl alcohol and acetate ions in acetic acid. In neither of these substitutions did they isolate the first-order reaction for both halides, but they showed that acetolysis which contained a first-order reaction led to mixtures of acetates, and that the heterogeneous substitution of the isomeric chlorides by means of silver acetate gave mixtures of the methylallyl acetates which were of similar composition for both halides. On the other hand, they did establish conditions for the second-order substitution of both chlorides in the case of alcoholysis, and on examining the products they found, just as we did, that each chloride gives only an ethoxy-compound of its own type of constitution. Similar results were obtained for acetolysis with acetate ions in acetone or acetic anhydride. In a later paper (*ibid.*, 1944, **66**, 421) Young and Andrews reported on an analogous investigation of the hydrolysis of the isomeric chlorides in aqueous or aqueous-alcoholic media. From a study of the reaction kinetics and products in the presence of varying concentrations of alkali, they concluded that the secondary chloride reacts only by the unimolecular mechanism under these conditions, to give a mixture of alcohols containing about 65% of the secondary isomer, while the primary chloride has a tendency to follow the bimolecular mechanism, and gives, under conditions most favourable to bimolecular substitution, high proportions of the primary alcohol. Evidence was obtained that the first-order (solvolytic) reaction of the primary chloride is in part a bimolecular reaction with the solvent. The heterogeneous hydrolysis with an aqueous suspension of silver oxide gave a mixture of alcohols from both halides, the composition of the mixture being similar, but not identical, in the two cases.

A notable outcome of the work described in this paper, and also that of Young and his co-workers, is that bimolecular substitution with rearrangement (S_N2') does not occur under the conditions employed. There is, of course, an obvious correspondence between this result and that of Part I in which we failed to find a bimolecular isomeric rearrangement. The significance of both results is discussed in the following paper.

Experimental.

γ- and α-Methylallyl Chlorides.—The pure chlorides were isolated from mixtures of the two isomers by fractional distillation (Kharasch, Kritchevsky, and Mayo, *J. Org. Chem.*, 1937, **2**, 489). It was found expedient to use for this purpose two different mixtures, each rich in either γ- or α-methylallyl chloride. γ-Methylallyl chloride (b. p. 84·0—84·2°/760 mm.; $n_D^{20°}$ 1·4350) was thus obtained from crotyl alcohol and hydrogen chloride, while α-methylallyl chloride (b. p. 63·9—64·2°/760 mm.; $n_D^{20°}$ 1·4151) was isolated from the addition product of butadiene and hydrogen chloride (Kharasch *et al.*, *loc. cit.*). Neither chloride was isomerised by being boiled under reflux for 5 hours, either alone or in solution in acetone.

Ethyl γ- and α-Methylallyl Ethers.—A mixture of γ- and α-methylallyl bromide (110 ml.) obtained from α-methylallyl alcohol and hydrogen bromide (Young and Lane, *J. Amer. Chem. Soc.*, 1937, **59**, 2051) was mixed with dry ethyl alcohol (200 ml.) and boiled under reflux for 2 hours, the solution being kept substantially neutral by frequent titration with alcoholic sodium ethoxide, using phenolphthalein as indicator. The product was diluted with an equal volume of water and saturated with sodium chloride, and the mixture was distilled. Distillation was continued until a test sample of distillate gave no separation into layers on dilution with water. The whole distillate obtained up to this point was diluted with an equal volume of water, and the upper layer was separated and washed with water, the washings being added to the aqueous layer. An equal volume of water was added to the aqueous

portion, and, after being saturated with salt, the mixture was fractionally distilled as before. This process was repeated until no ether separated from the first few ml. of distillate on addition of water. The crude ether thus obtained (124 ml.) was dried (P_4O_{10}) and distilled from barium oxide. Repeated fractional distillation to constant refractive index gave ethyl α-methylallyl ether, b. p. 75·5—76·0°/760 mm., $n_D^{25°}$ 1·3872, and ethyl γ-methylallyl ether, b. p. 100—100·5°/760 mm., $n_D^{25°}$ 1·4020 (Found, for a mixture of the two ethers: C, 71·8; H, 11·7. Calc.: C, 72·0; H, 12·0%). The refractive index–composition plot for synthetic mixtures of the isomeric ethers was shown to be linear.

Isolation and Examination of Ethers from the Etholysis of γ- and α-Methylallyl Chlorides.—The alcoholysis of each of the isomeric chlorides was carried out in absolute ethyl alcohol under two sets of experimental conditions, namely, (*a*) in substantially neutral solution, and (*b*) in 2·7N-solution of sodium ethoxide—these being conditions conducive to the operation of the unimolecular (S_N1) and the bimolecular (S_N2) mechanism respectively. The aim of our isolation technique was to obtain samples of the ethers, the composition of which would correspond to the proportions of ethyl γ- and α-methylallyl ether produced under the conditions stated. The method adopted (see below) has been shown to give reliable results by carrying out the procedure with synthetic mixtures containing the two ethers in known proportions. For the solvolytic reaction, the halide (10 ml.) was dissolved in dry ethyl alcohol (100 ml.) and boiled under reflux for 72 hours, the solution being kept nearly neutral by frequent titration with alcoholic sodium ethoxide, phenolphthalein being used as indicator. Bimolecular alcoholysis of each chloride (10 ml.) was carried out by boiling it under reflux with 2·7N-sodium ethoxide in ethyl alcohol (100 ml.) for 12 hours.

In illustration of the experimental method, details are given below of the isolation of the ether mixture formed by the solvolysis of γ-methylallyl chloride in ethyl alcohol. The reaction mixture, after dilution with an equal volume of water, was saturated with sodium chloride and distilled to give the following fractions: (1*a*) 5 ml., b. p. 75—78°; (1*b*) 7 ml., b. p. 78—81°; (1*c*) 10 ml., b. p. 81—83°; (1*d*) 10 ml., b. p. 83—85°; (1*e*) 40 ml., b. p. 85—88°. With water (equal volume), (1*a*) and (1*b*) gave an upper layer of ether, which was separated and washed with water, whilst (1*c*), (1*d*), and (1*e*) gave no separation of layers. Fractions (1*c*), (1*d*), (1*e*), the washings from (1*a*) and (1*b*), and an equal volume of water, were combined, saturated with salt, and redistilled: (2*a*) 3 ml., b. p. 80—82°; (2*b*) 6 ml., b. p. 82—83°, (2*c*) 10 ml., b. p. 83—85°; (2*d*) 25 ml., b. p. 85—89°. With water (2*a*) gave an upper layer which was washed with water, whilst (2*b*), (2*c*), and (2*d*) gave no separation. Fractions (2*b*), (2*c*), and (2*d*), the washing from (2*a*), and an equal volume of water were combined, saturated with salt, and redistilled: (3*a*) 2 ml., b. p. 82—84°; (3*b*) 4 ml., b. p. 84—87°; (3*c*) 6 ml., b. p. 87—88°. With water (3*a*) gave an upper layer, and the washings, together with fractions (3*b*) and (3*c*), were again treated as above: (4*a*) 1 ml., b. p. 84—85°; (4*b*) 1 ml., b. p. 85°. With water (4*a*) gave a very small upper layer which was separated and washed with water.

The top layers (crude ethers, totalling 8·5 ml.) from (1*a*), (1*b*), (2*a*), (3*a*), and (4*a*) were distilled completely, first from fused barium oxide, and then from sodium. The refractive index ($n_D^{25°}$ 1·4008) of the final distillate (8·0 ml.) showed it to have the following composition: ethyl γ-methylallyl ether 92%, ethyl α-methylallyl ether 8%.

The percentage compositions of the various halide and ether mixtures were in all cases determined from their refractive indices. The results are summarised below:

Reactant (Halide).		Condition of reaction.*	Product (Ether).	
$n_D^{25°}$.	% of primary.		$n_D^{25°}$.	% of primary.
1·4123	0	1	1·3993	82
1·4123	0	2	1·3872	0
1·4324	100	1	1·4008	92
1·4324	100	2	1·4020	100
1·4260	68	1	1·4007	91
1·4179	28	2	1·3915	29

* 1 = Solvolysis in EtOH; 2 = Reaction with OEt in EtOH.

We wish to acknowledge with gratitude our indebtedness to Professor C. K. Ingold, F.R.S., for much valued help and encouragement during the course of the work described in this and the preceding paper.

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3. *Rearrangement and Substitution in Anionotropic Systems. Part III. Mechanism of, and Equilibrium in, Anionotropic Change.*

By A. G. Catchpole, E. D. Hughes, and C. K. Ingold.

The discussion given by Burton and Ingold in 1928 of the subjects indicated in the title is modernised and extended. It is shown that the general mechanism both of isomerisation and of substitution with rearrangement in anionotropic systems is dependent on ionisation, although an intramolecular mechanism can make its appearance in certain special cases of isomerisation. Bimolecular rearrangement appears to be excluded, and a reason for this is suggested. The distinctions between the kinetic and thermodynamic control of rearrangement are emphasized.

The theory of conjugation and hyperconjugation energy is used in the discussion of anionotropic equilibria, with results which are qualitatively satisfactory and hold some promise of successful quantitative development.

(1) *Mechanism of Rearrangement in Anionotropic Systems.*

SINCE the appearance in 1928 of Burton and Ingold's paper on anionotropy, no revised general discussion of the subject has been published, although in the meantime it has passed through quite a history. This has been partly a written history * of direct investigations by Burton, Meisenheimer, Kenyon, Young, Winstein, and others. To a large extent, however, it has been an unwritten history arising out of the bearing on the subject of our knowledge of nucleophilic substitution, as this has developed in the intervening years. The primary effect of the more recent knowledge was to introduce previously unsuspected ambiguities of interpretation. Therefore, new experimental work was undertaken, the results of which were summarised by Hughes in 1941, and are now recorded in the accompanying papers by Catchpole and Hughes. As this work succeeded in its object of resolving the difficulties referred to, some further discussion seems profitable.

It was assumed by Burton and Ingold (*J.*, 1928, 904) that the rate-controlling step in anionotropic change is the separation of the mobile group (always an electron-attracting group such as halogen or acyl) as a fully dissociated anion. The residual carbonium ion was then necessarily mesomeric, its distributed positive charge being capable of concentration, for the purposes of ionic recombination, on either of two alternative carbon atoms. It made no difference of principle whether the anion, which in the final, rapid stage combined with the carbonium ion, was one of those formed in the original ionic dissociation or was some other anion, possibly of a different kind, specially provided for the purpose: the mechanisms of the strictly isomeric change, and of the substitution of the mobile group by a group derived from a different anion, with a completely analogous rearrangement of the unsaturated system, were regarded as identical in all essentials. This mechanism clearly belongs to the type of substitution mechanism which was subsequently recognised as being of wide occurrence in saturated compounds, was termed unimolecular nucleophilic substitution, and was labelled S_N1. It is formulated for the anionotropic case (using the curved bond-sign to represent a distributed electron pair) in the following scheme, in which $\bar{Y}$ may represent any anion, not excluding $\bar{X}$:

$$R{\cdot}CHX{\cdot}CH{:}CH_2 \longrightarrow \bar{X} + [R{\cdot}CH\overset{\frown}{\text{---}}CH\overset{\frown}{\text{---}}CH_2]^+ \xrightarrow{\bar{Y}} \begin{cases} R{\cdot}CHY{\cdot}CH{:}CH_2 \\ R{\cdot}CH{:}CH{\cdot}CH_2Y \end{cases} \ldots (S_N1)$$

(*a*) *Non-appearance of Bimolecular Rearrangement.*—It was a natural outcome of the work on saturated compounds that Hughes later considered the application to rearrangement and substitution in anionotropic systems of the other homogeneous mechanism which had been found general for substitution at a saturated carbon atom, namely, bimolecular nucleophilic substitution, S_N2 (*Trans. Faraday Soc.*, 1938, **34**, 194). He pointed out that this type of mechanism might lead not only to substitution of the ordinary type, S_N2, that is, without rearrangement, but also to substitution with rearrangement, S_N2'. The latter possibility provided a simple, and superficially attractive, explanation of an important observation by Meisenheimer which will be discussed presently. In the following scheme $\bar{Y}$, as before, intended to denote any anion, not excluding $\bar{X}$:

$$\bar{Y} + R{\cdot}CHX{\cdot}CH{:}CH_2 \begin{cases} \longrightarrow R{\cdot}CHY{\cdot}CH{:}CH_2 + \bar{X} \ldots\ldots (S_N2) \\ \longrightarrow R{\cdot}CH{:}CH{\cdot}CH_2Y + \bar{X} \ldots\ldots (S_N2') \end{cases}$$

However, the work of Catchpole and Hughes (*Trans. Faraday Soc.*, 1941, **37**, 629; this vol., pp. 1, 4), confirmed by that of Roberts, Young, and Winstein (*J. Amer. Chem. Soc.*, 1942, **64**, 2157; cf. Young and Andrews, *ibid.*, 1944, **66**, 421), shows that, although the simple substitution mechanism, S_N2, can readily be observed, the substitution with rearrangement, S_N2', apparently cannot be realised.

* A useful review covering a part of the subsequent work has been given by H. B. Watson (*Ann. Reports*, 1938, 233).

It is relevant to enquire to what extent this finding is likely to prove general. The most obvious plan by which one might endeavour to suppress reaction S_N2, in the hope of observing reaction S_N2', would be to build up a condition of steric inhibition to the transition state of the substitution S_N2. The α-substituent, R, which in the experiments mentioned was a methyl group, already does this to some extent. However, our knowledge of aliphatic substitution in general, and Catchpole and Hughes's work on substitution in alkylated allyl compounds in particular, show that the introduction of another hydrocarbon radical in the α-position would render ionisation, which amongst allyl compounds generally can only be suppressed in a limited range of conditions, well-nigh impossible to avoid: the dominant mechanism would then be S_N1. The same is true if the α-alkyl group should be replaced by an α-aryl group. Substitution in the β-position would affect the α- and γ-positions similarly, and substitution in the γ-position would act in the wrong direction. The most hopeful possibility would be to use a *tert.*-butyl group for R, an experiment which we hope to try; but whether this works or not, it is already evident that mechanism S_N2' is not going to apply in the most simple and typical cases of anionotropic systems.

Although this result was not anticipated, it seems, in retrospect, reasonable in relation to the broad picture of substitution which has been built up since 1926. This shows that at a saturated carbon atom nucleophilic substitution is the general rule, whilst at an unsaturated, and, in particular, an aromatic, carbon atom electrophilic substitution is the prevalent mode. In more detail, it appears that a carbon atom which possesses only σ-electrons is fundamentally rather sensitive to nucleophilic, but is much less sensitive to electrophilic, reagents. Since all the valency electrons of such a carbon atom are mainly localised between two nuclei, they are to that extent protected from electrophilic attack; and since their charge density is maximal along the lines of the geometrical bonds, they leave, in between, regions of lower electron density, through which a nucleophilic reagent may make its approach. On the other hand, it appears that a carbon atom possessing π-electrons is less sensitive to nucleophilic, and more so to electrophilic, reagents. Since π-electrons are unprotected laterally to the plane of the adjacent atoms, they may be expected to be vulnerable to electrophilic reagents; furthermore, they have their maximum charge density in just that direction in which, but for their presence, it would be sterically most natural for a nucleophilic reagent to approach the carbon nucleus. These, of course, are general considerations, and are subject to modification in the presence of a strong electrostatic deformation of the π-electrons as in the carbonyl group or a nitro-substituted benzene nucleus. We assume that in the anionotropic case the π-electrons of the double bond to a considerable extent protect the γ-carbon atom from the attack of the nucleophilic reagent $\bar{Y}$, thus inhibiting bimolecular rearrangement by mechanism S_N2', at least in the absence of strong electrostatic deformation or of other special influences. These stereo-electronic considerations clearly have some bearing on the π-bond theory of Dewar (*J.*, 1946, 406).

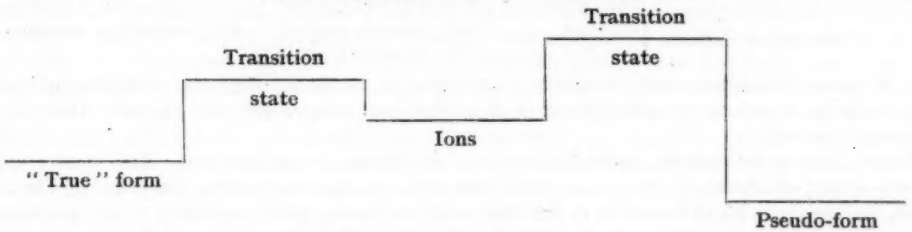
(*b*) *Kinetic and Thermodynamic Control of Rearrangement.*—We may now consider the observation of Meisenheimer, the interpretation of which for some time remained equivocal.* It was found by Meisenheimer and Link (*Annalen*, 1930, **479**, 221) that γ-phenylallyl (cinnamyl) chloride, the more thermodynamically stable member of a pair of anionotropic chlorides, on treatment with potassium acetate in acetic acid, gave a mixture of α- and γ-phenylallyl acetate, even though, after a considerably longer period in the same solvent (or a sufficient period in any polar solvent), the α-phenylallyl acetate isomerised completely to γ-phenylallyl acetate, the more thermodynamically stable member of the pair of acetates. Analogously, γ-phenylallyl bromide with alcoholic alkali yielded a mixture of ethyl α-phenylallyl ether and ethyl γ-phenylallyl ether; in this case no direct interconversion of the ethers was realised, but by analogy, as well as for theoretical reasons (see below), we should expect the equilibrium between them to be entirely in favour of the γ-phenylallyl compound. The formation of the two acetates was further investigated by Meisenheimer and Beutter (*ibid.*, 1934, **508**, 58). They found that the solvolytic reaction of γ-phenylallyl chloride in acetic acid, with no salts present, gave a qualitatively similar result, the mixture of acetates, as first formed under these conditions, containing 18% of the α-phenylallyl compound. The addition of those soluble metallic acetates which yielded, after the interaction, soluble metallic chlorides (so that the system remained homogeneous) decreased this proportion; as also did the addition of water to the acetic acid; whilst metallic acetates which gave precipitated metallic chlorides increased the figure. Approximate first-order kinetics were established for the change γ-phenylallyl chloride ⟶

* The difficulty of this matter was first made apparent in a discussion given by Baker ("Tautomerism", Routledge, 1934, p. 232).

total acetate in acetic acid containing lithium acetate (homogeneous system). The reaction was accelerated by added water or lithium chloride.

At first the bimolecular mechanism, S_N2', appeared to provide a simple explanation of these observations, and Roberts, Young, and Winstein (*loc. cit.*) were inclined to consider this as a serious possibility. We hold, however, that, in view of Catchpole and Hughes's conclusions, the theory can no longer be entertained. The exclusion of this possibility enables the alternative view to be advanced with some confidence, namely, that Meisenheimer was dealing with a case in the field of anionotropy of the phenomenon, familiar in prototropy, of the distinction between kinetic and thermodynamic control in ion-recombination. The close analogy between the two cases provides, we think, a definite piece of circumstantial evidence in favour of the ionisation picture of anionotropy.

In the field of prototropy the phenomenon is exhibited in an extreme form in pseudo-acids. If a solution of an alkali metal salt of such a compound is acidified, the mesomeric anion reassociates with a proton more quickly to form the true acid, but with a greater diminution of free energy to form the pseudo-acid; and the true acid will yield the common ions much faster than will the pseudo-acid. The accompanying schematic energy diagram shows these relationships: kinetic control of the proportions of the isomerides is regulated by the top two



levels, thermodynamic control by the bottom two. Thus, by operating speedily at a low temperature we may isolate *aci*-phenylnitromethane, although this is the thermodynamically less stable form and eventually must re-ionise and isomerise to the pseudo-form. Less extreme examples are known amongst isomeric $\alpha\beta$- and $\beta\gamma$-unsaturated carbonyl compounds. The former are commonly the thermodynamically more stable isomerides, though, by acidification of salts, the latter may be first formed in considerably more than their equilibrium proportions. In view of these analogies, Meisenheimer's phenomenon would seem to require the assumption that the γ-phenylallyl halide first forms a mesomeric carbonium ion, and that this combines with an anion, such as acetate or ethoxide, in the two possible positions at comparable speeds, thus first producing the α-phenylallyl compound in far more than its equilibrium proportion, though the re-ionisation of this substance must eventually yield the γ-phenylallyl isomeride almost exclusively.

The details fit satisfactorily into this picture. Effects due to highly polar molecular solutes and to ionised salts in dilute solution on rates of ionisation are, for electrostatic reasons, qualitatively similar; and so also they must be on rates of ion recombination; such effects are generally greater the smaller the free energy difference between the molecule and its ions (Bateman, Church, Hughes, Ingold, and Taher, *J.*, 1940, 979). The direction of the influence on ion recombination is retardation, and this effect is expected to be exerted more strongly on the formation of the more readily ionisable α-phenylallyl compound. This would explain the effect of added water and salts on the proportion in which α-phenylallyl acetate is formed, except for those systems which become heterogeneous, when a surface reaction is possible. The effect of dipoles and ions on ionisation is accelerative. Since the rate of the total reaction is controlled by an ionisation, we may readily understand the approximate first-order kinetics, the acceleration produced by added water, and the considerable positive salt effect of lithium chloride (Bateman *et al.*, *loc. cit.*). For a bimolecular reaction these effects would be much smaller and in the opposite direction.

It is also possible to interpret the supplementary investigation which Meisenheimer and Link carried out (*loc. cit.*) on the acetolysis of γ- and α-ethylallyl chlorides, which, although tautomeric, are both stable enough to be studied separately. Under the conditions used, corresponding acetates underwent no measurable interconversion. With acetate ions in acetic acid the following results were obtained:

Primary chloride ⟶ 93% primary acetate + 7% secondary acetate
Secondary chloride ⟶ 40% primary acetate + 60% secondary acetate

With silver acetate as the reagent the results were as follows:

Primary chloride ⟶ 57% primary acetate + 43% secondary acetate
Secondary chloride ⟶ 54% primary acetate + 46% secondary acetate.

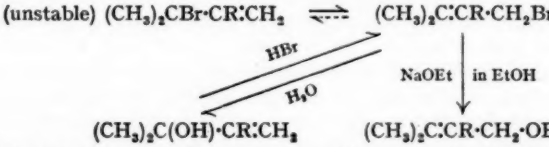
We assume that the smaller tendency to ionisation possessed by these aliphatic chlorides lends considerably greater importance to the bimolecular mechanism of substitution when comparison is made with γ-phenylallyl chloride; this is in agreement with well-established principles. But, according to the findings of Catchpole and Hughes, and of Roberts, Young, and Winstein, bimolecular substitution can produce only that acetate which corresponds in structure to the chloride. That is why, in the acetate ion reaction, the two chlorides give different results. However, substitution with the aid of a silver salt, although heterogeneous, is closely analogous in mechanism to the homogeneous reaction S_N1 (Cowdrey, Hughes, Ingold, Masterman, and Scott, *J.*, 1937, 1252). Thus it is that, in the silver acetate reaction, both chlorides give a nearly common result. If we provisionally accept this result as furnishing the kinetically controlled ratio (55 : 45) in which the two acetates are formed from the mesomeric carbonium ion, a tentative analysis of the acetate ion reaction may be made as follows:

Primary chloride { by S_N1 ..... 9% primary acetate + 7% secondary acetate
by S_N2 ..... 84% primary acetate

Secondary chloride { by S_N1 ..... 40% primary acetate + 33% secondary acetate
by S_N2 ..... 27% secondary acetate

It is, of course, consistent with the general picture of nucleophilic aliphatic substitution that the proportion of bimolecular substitution S_N2 comes out greater for the primary than for the secondary chloride.

Some older observations similarly receive a satisfactory explanation. The most complete of these is that of Claisen (*J. pr. Chem.*, 1922, **105**, 65), who showed that γγ-dimethylallyl bromide, which, like γ-phenylallyl bromide, is the thermodynamically stable member of the anionotropic system to which it belongs, on treatment with dry alcoholic sodium ethoxide gave ethyl γγ-dimethylallyl ether, but with water or dilute aqueous sodium carbonate produced αα-dimethylallyl alcohol, from which γγ-dimethylallyl bromide could be regenerated by treatment with hydrogen bromide (formulæ below, R = H). Similar transformations were carried through with the β-methyl homologues (R = Me):



Here the γγ-dimethylallyl structure is the thermodynamically stable one (see below), although only the bromide system, not the alcohol system or ether system, is mobile under the conditions employed. However, in unimolecular substitution, which, as Catchpole and Hughes's investigation proves (this vol., p. 4), will occur when water or dilute aqueous alkali acts upon the bromide, kinetic control of ion-recombination favours the αα-dimethylallyl product. The appearance, on the contrary, of a γγ-dimethylallyl product in the bimolecular substitution, which, as Catchpole and Hughes's work also shows, is to be expected when the reagent is alcoholic sodium ethoxide, is necessitated by the non-existence of bimolecular replacement with rearrangement, S_N2'. Once again a thermodynamically unstable isomeride is formed from the mesomeric carbonium ion in far more than the equilibrium proportion.

(*c*) *Status of Intramolecular Isomerisation.*—The other main ambiguity to be dealt with arises from the circumstance that, besides mechanisms S_N1 and the hypothetical mechanism S_N2', a third view of anionotropic rearrangements has always been possible (cf. Hughes, *loc. cit.*), namely, that they are intramolecular. This idea has been much discussed by Kenyon and his collaborators. Balfe and Kenyon have drawn a sharp distinction between non-isomeric replacements involving rearrangements and the corresponding isomeric changes (*Trans. Faraday Soc.*, 1941, **37**, 723). For the former they adopt (as Kenyon has done consistently) the ionisation scheme labelled S_N1 on p. 9. But now, desiring to restrict its application to non-isomeric replacements, they introduce a subtle difference into the formulation by (i) replacing the single arrow on the left-hand side of the above-written scheme, S_N1 (p. 9), by the sign for a reversible reaction, and (ii) allowing $\bar{Y}$ to represent, not any anion, but any anion *excepting* $\bar{X}$. To us it does not seem likely that the mesomeric carbonium ion should be able to combine at either end

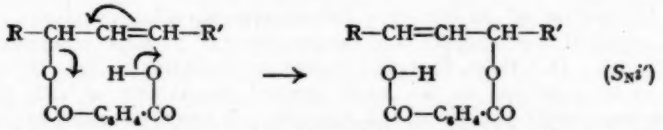
with $\bar{Y}$, but only at one end with $\bar{X}$, when these anions might be, say, an acetate and a benzoate ion, or two even more closely similar ions. Indeed, the suggested discrimination appears untenable when it is remembered that X and Y might be interchanged; for by agreed hypothesis, the same carbonium ion would be an intermediate when (to continue with the same example) acetate ions act upon an allyl benzoate as when benzoate ions act on an allyl acetate.

Kenyon and his collaborators have adduced important evidence for the ionisation mechanism of non-isomeric replacements with rearrangement by their discovery that optical activity dependent on asymmetry which would be destroyed by ionisation is actually lost in the rearrangement process. In an example such as the solvolysis of optically active $\alpha\gamma$-dimethylallyl hydrogen phthalate by formic acid, acetic acid, methyl alcohol, etc., the symmetry of the anionotropic system renders it impossible to prove directly that rearrangement has occurred; but Balfe, Hills, Kenyon, Phillips, and Platt showed (*J.*, 1942, 556), not only that the solvolytic product was completely, or nearly completely, racemised, but also that the original ester recovered from an incomplete reaction was often largely racemised, just as though most of it had once been ionised. It is significant that with the best ionising solvents, such as formic acid, the activity of the product was vanishing, whilst it was only with poor ionising solvents, such as *n*-butyl alcohol, that racemisation was appreciably incomplete (greatest observed activity, 9%). In the light of Catchpole and Hughes's results, this residual activity may perhaps be interpreted as arising from bimolecular substitution without rearrangement (S_N2). Consistently the sign of the activity was found to represent an inverted configuration (Cowdrey, *et al.*, *loc. cit.*). For some similar solvolyses of γ-methyl-α-*n*-propylallyl chloride, and the corresponding hydrogen phthalate, Arcus and Kenyon ingeniously proved (*J.*, 1938, 1912) that the small residual activity found in some of the solvolysis products (maximum 2%) was really due to substitution without rearrangement; they did this by showing that the activity was lost when the double bond was reduced, a process which must destroy asymmetry in the original, but not in the rearranged, structure.

The position with respect to the isomeric changes is less simple. Balfe and Kenyon follow Arcus and Kenyon in regarding them as intramolecular, essentially on evidence earlier presented by Kenyon, Partridge, and Phillips (*J.*, 1937, 207). Arcus and Kenyon refer to those authors as having proved, in the example of the isomerisation of α-phenyl-γ-methylallyl compounds to the corresponding γ-phenyl-α-methylallyl derivatives, " that the migrating anion is not kinetically free since there is a high retention of asymmetry " on rearrangement. We think that this is an over-simplification of Kenyon, Partridge, and Phillips's findings, which it is necessary to restate in more detail.

These authors studied four α-phenyl-γ-methylallyl derivatives, namely, the alcohol in acid conditions (presumably the active entity is the hydroxonium ion), the *p*-nitrobenzoate, the acetate, and the hydrogen phthalate. Now a necessity for the provision of any proof of an *intramolecular* mechanism is to separate the rearranging molecules from one another by operating in a solution at least so dilute that the specific rate shall be independent of the concentration. The alcohol was examined in dilute aqueous acetic acid, and, though the rate was not studied, we may assume that the dilution was suitable; but the retention of optical activity in the product was only 3%. The *p*-nitrobenzoate gave a substantial retention of activity when isomerised in the fused state; but on isomerisation in moderately dilute solution in chloroform it gave a completely inactive γ-phenyl-α-methylallyl ester. The acetate was studied in more concentrated solution in acetic acid, and the product showed a 14% retention of activity. Only in the case of the hydrogen phthalate was a large degree of optical activity retained after isomerisation, not only in the fused state, but also (up to 58%) in solutions of demonstrably sufficient dilution.

It would thus appear that the hydrogen phthalate is a special case, and Hughes has already suggested that the free carboxyl group is involved in its racemisation (*Trans. Faraday Soc.*, 1941, **37**, 725). We here slightly modify his scheme by making a proton transfer between the carboxyl groups (internal acid catalysis assisting fission of the C–O bond) essential to the change:



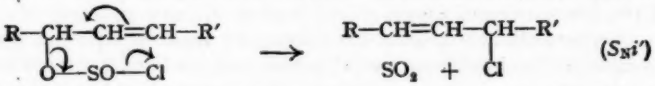
(S_Ni')

We do this in order to accommodate the observation that the salts (*i.e.*, the anions) of the hydrogen phthalates are much less prone to isomerise than are the free acids. This fact is, of

course, consistent with the exclusion of mechanism S_N2' in isomerisation, as indicated by Catchpole and Hughes (this vol., p. 1), since such a rearrangement of the anion would be an internal S_N2' reaction. The type of internal mechanism which the above formulæ illustrate is labelled S_Ni' because it is related to the substitution mechanism S_Ni of Cowdrey *et al.*—internal rearrangement leading to group replacement on a single carbon atom—exactly as the hypothetical mechanism S_N2' is related to mechanism S_N2.

Naturally mechanism S_Ni' is not in principle excluded from participation in the rearrangement of halides or of simpler esters, such as *p*-nitrobenzoates. However, the mechanism does not seem usually to play a major rôle for such reactions in dilute solution. A number of general circumstances concerning anionotropic isomerisation would be difficult to accommodate on a purely intramolecular picture of the reaction, for instance, the solvent and salt effects to which reference is made later. Probably the most notable single point which arises in this connection is Burton's demonstration (*J.*, 1929, 1650) that the isomerisation of α-phenylallyl *p*-nitrobenzoate could be largely diverted in the direction of a non-isomeric substitution with rearrangement by the introduction of acetate ions into the solution in which it was taking place. Balfe and Kenyon's remark on this subject is curious. They say: " The argument, that the rearrangement involves complete ionic dissociation, because in the presence of acetate ions α-phenylallyl *p*-nitrobenzoate yields cinnamyl acetate, . . . is shown to be invalid, because this reaction is a replacement and not a rearrangement ". We have already remarked that, if the formation of the carbonium ion is a step on the way to a replacement involving a structural change of the anionotropic system—and Balfe and Kenyon agree, and have helped to prove, that it is—then it must also be a step towards isomeric rearrangement: there is no difference of principle between the two cases. Of course, one can picture an intramolecular rearrangement which is so rapid that the ionisation has no time to occur; but if this were true, Burton would not have been able to divert the reaction.

Mechanism S_Ni' appears again amongst the replacements with rearrangement which take place on the conversion of a substituted allyl alcohol into mixtures of isomeric halides by means of reagents such as hydrogen halides, phosphorus halides, and thionyl chloride. The reactions of α- and γ-methylallyl alcohols with hydrogen bromide and phosphorus tribromide have been studied by Young and Lane (*J. Amer. Chem. Soc.*, 1937, **59**, 2051; 1938, **60**, 847), and those of α- and γ-ethylallyl alcohols with hydrogen chloride and thionyl chloride by Meisenheimer and Link (*Annalen*, 1930, **479**, 211). The results obtained with the hydrogen and phosphorus halides can be satisfactorily correlated, as Young and Lane have shown, by mechanisms identical with those labelled S_N1 and S_N2 by Cowdrey, Hughes, Ingold, Masterman, and Scott for the corresponding substitution reactions of saturated alcohols (*loc. cit.*). Mechanism S_N1 involves the formation of the carbonium ion; and since in the case of the substituted allyl compounds this ion is mesomeric, the mechanism produces from either of two isomeric alcohols the same mixture of isomeric halides. Mechanism S_N2 involves the attack by halide ion on an oxonium ion or phosphorous ester halide and proceeds without rearrangement of the anionotropic system; no mechanism S_N2' requires to be assumed. As with saturated alcohols, so also with these allyl alcohols, the introduction of pyridine into reactions involving phosphorus halides brings mechanism S_N2 into special prominence, with consequential reduction in the amount of rearrangement accompanying substitution. For these reagents neither mechanism S_Ni nor the analogous S_Ni' clearly appears. However, with thionyl chloride, which, as shown by Cowdrey *et al.*, is the best reagent for bringing mechanism S_Ni into prominence in the reactions of saturated alcohols, Meisenheimer and Link obtained this unusual result, namely, that their primary alcohol gave mainly the secondary chloride and their secondary alcohol mainly the primary chloride. As Roberts, Young, and Winstein have already noted (*loc. cit.*) this seems rather a clear indication of the rearrangement of a first-formed chlorosulphinic ester in accordance with mechanism S_Ni':



(*d*) *General Mechanism of Anionotropic Rearrangement.*—Our conclusions are, then, that mechanism S_N2' rarely if ever appears, and mechanism S_Ni' becomes prominent only in rather special circumstances. It follows that the ionisation mechanism, S_N1, though not the only mechanism, is to be regarded as the most general mechanism of both the isomeric and non-isomeric rearrangements of anionotropic systems. It seems desirable to put the arguments in favour of this mechanism more positively. In summary, they are as follows.

(i) Rearrangement, either isomeric or non-isomeric, in R·CHX·CH:CH·R′ is strongly

correlated with the general chemistry of the group X, in particular, with its tendency to separate from carbon as the anion $\bar{X}$ (Burton and Ingold, *loc. cit.*). This becomes intelligible only if X is required to separate as $\bar{X}$ in the rate-controlling stage of reaction. The relationship indicated is not one which is normal for internal isomeric change (cf., *e.g.*, the known internal changes of allyloxybenzene and its derivatives).

(ii) Rearrangement in R·CHX·CH:CH·R′ is kinetically facilitated very strongly by electron-releasing substituents R and R′ (Burton and Ingold, *loc. cit.*; Hughes, *Trans. Faraday Soc.*, 1941, **37**, 627). Speaking generally, the effect is as important for isomerisation as for non-isomeric rearrangement, and is as prominent for anionotropic systems as a whole as it is for the ordinary unimolecular nucleophilic substitutions of saturated compounds, where it is agreed that the rate-controlling step is the formation of a carbonium ion. No other substitution mechanism is so sensitive to polar constitutional influences (cf. Polanyi, *Chem. and Ind.*, 1943, 166).

(iii) Kenyon and his collaborators have shown that both the isomerisations and non-isomeric rearrangements of optically active systems R·CHX·CH:CH·R′ in dilute solution are normally accompanied by a large degree of racemisation; though they have also discovered an explicable exception in the field of isomerisations (see above). A large degree of racemisation (not necessarily complete racemisation—cf. Cowdrey *et al.*) may be regarded as diagnostic for mechanism S_N1.

(iv) Meisenheimer and his collaborators have shown that both the isomerisation and substitution of α-phenylallyl esters in solution follow the first-order rate law, except for deviations explicable as salt effects. In the substitution, the stoicheiometric reaction was essentially with added anions, so that the reaction may be classed as non-solvolytic. Catchpole and Hughes, and Roberts, Young, and Winstein have established similar kinetics for substitutions of α-methylallyl chloride, and this halide is sufficiently insensitive to alkali to render improbable a bimolecular solvolytic interpretation. For the substitutions with rearrangement these results may be regarded as definitely diagnostic of mechanism S_N1. For the isomerisation they are not diagnostic by themselves, but Catchpole and Hughes have excluded the bimolecular interpretation by showing that the anion derived from the system is not a catalyst. (There is evidence of the incursion of acid catalysis in certain circumstances, but this can be explained as arising from a pre-equilibrium involving the catalysing acid and unshared electrons of the mobile group, the original anionotropic system being thus converted into a more mobile one. Acid catalysis must be mentioned in any general statement of the kinetic findings, but it hardly bears, except as stated, on the question of the mode of rearrangement of the unsaturated system.)

(v) Catchpole and Hughes have shown that the first-order substitutions of two isomerides of form R·CHX·CH:CHR′ and R·CH:CH·CHXR′ produce nearly the same mixture of isomeric substitution products (above). This is diagnostic for the S_N1 mechanism of the substitution with rearrangement, and also for the substitution without rearrangement which occurs under the same conditions. It is not inconsistent that, as Meisenheimer in particular proved, the mixture of isomerides formed in such conditions may not be the equilibrium mixture (above).

(vi) It has been shown in the example of α-phenylallyl esters by Burton and Ingold (*loc. cit.*) and by Meisenheimer, Schmidt, and Schäfer (cf. this vol., p. 1) that the rate of isomerisation in solution is very sensitive to the solvent, and in general increases with the dielectric constant of the solvent. A similar effect has been established for alcohol–water mixtures by Catchpole in the example of the non-isomeric substitutions of various substituted allyl chlorides (Thesis, Univ. London, 1942). The magnitude and direction of these effects would be difficult to reconcile with any but a predominating or exclusive S_N1 mechanism.

(vii) Meisenheimer and Beutter have shown (*loc. cit.*) that the isomerisation of an allyl acetate in acetic acid is accelerated by small additions of salt or of water. They have also proved that the non-isomeric substitution of an allyl chloride by acetate ions is accelerated by the inert salt, lithium chloride, and also by small additions of water (above). These effects, due to added ions or dipoles, are of the order of magnitude to be expected of a reaction dependent on primary ionisation, and they would be very difficult to reconcile with any other mechanism.

(viii) Burton has linked the mechanism of isomerisation to the S_N1 mechanism of substitution with rearrangement by showing that the former process may be partly diverted in the direction of the latter by adding foreign anions. He has further shown that the diverted reaction is not a step-wise rearrangement and substitution, and that it must therefore be simultaneous with the undiverted isomerisation (above). There is abundant evidence that the diverted reaction is

unimolecular, and therefore that the carbonium ion is formed fast enough to provide a route for the isomerisation.

The general shape of the evidence, as it stands at present, is shown in the following tabular conspectus of these arguments and inferences :

Method of experiment.	Inference. Isomerisation.	Substitution.
(i) Facilitation according to the stability of X^-	S_N1 or S_N2	S_N1 or S_N2
(ii) Strong acceleration by electron release from R	S_N1	S_N1
(iii) Optical activity (usually lost)	S_N1 usually	S_N1
(iv) Rate law (first-order, etc.)	S_N1 or S_Ni'	S_N1
(v) Common product-mixture in substitution	—	S_N1
(vi) Solvent effect (direction and sensitivity)	S_N1	S_N1
(vii) Effect of added ions and dipoles	S_N1	S_N1
(viii) Burton's diversion experiments	Same for both	

The tabulated inferences are those which might be drawn from the different lines of attack if each were the only source of evidence available. But if we take all the points together, it is clear that the fundamental inference is what is common to, or consistent with, them all: obviously we must conclude that there is only one general mechanism, *viz.*, the ionisation mechanism, S_N1, whatever may happen in special circumstances. It should again be emphasised that we are discussing reactions in solution, and not those undergone by materials in the fused, crystalline, or gaseous state.

(2) *Equilibrium in Anionotropic Systems.*

When Burton and Ingold originally discussed this subject, the resonance energy associated with conjugation had not yet been recognised, and hyperconjugation had still to be discovered. Consequently the only picture which could be given was in qualitative kinetic terms, which are incapable of quantitative development in the foreseeable future owing to the unavailability of sufficiently precise information concerning the transition states of reactions. The situations then dealt with can now, however, be more simply redescribed in terms of the energies of normal molecules, in terms that is to say, which, though still essentially qualitative, show the first vestiges of quantitative development, and are at any rate in the right form for quantitative treatment as soon as the factors of energy in normal molecules are understood in greater detail.

The simplest examples arise when an aryl, vinyl, or substituted vinyl radical is attached to the anionotropic system in such a way that it becomes conjugated with the anionotropic double bond in one of its possible positions. The energy effect of this conjugation will then count as a direct contribution to the free energy of one of the isomerides. No doubt other influences, constitutional and environmental, will affect the free energies of both isomerides, but the order of magnitude of the over-all differential effect will be correctly given if we neglect these other factors in comparison with the conjugation energy. It is probable also that the conjugation energy itself can only in first approximation be treated as a constant characteristic of the unsaturated system; and that it will in different cases be subject to modification from influences arising both from within the molecule and from the solvent: it is just this kind of influence about which we need more information, from the further study of heats of reaction and solution, before a quantitative theory can become possible. Nevertheless an assumed constant value will still serve to assess the order of magnitude of the effect.

For example, we know from experiment that in the γ-phenylallyl–α-phenylallyl system the equilibrium proportion of the α-phenylallyl isomeride is too small for experimental detection (Burton and Ingold; Meisenheimer; X = Hal or O·Acyl) :

$$C_6H_5\cdot CH{:}CH\cdot CH_2X \rightleftharpoons C_6H_5\cdot CHX\cdot CH{:}CH_2$$

The energy of conjugation of a phenyl group with a vinyl group is usually taken as 7 kilocals. (Pauling, " Nature of the Chemical Bond ", Cornell Press, 1940, p. 137). Neglecting other factors, we can calculate from this figure that at 300° K. the equilibrium proportion of the α-phenylallyl isomeride should be of the order of 0·001%. Alkyl-γ-phenylallyl systems are, of course, in substantially the same case.

Baker and Nathan produced the first evidence of the hyperconjugation existing between alkyl groups and double bonds (*J.*, 1935, 1844). The influence of this factor on the free energies of transition states was more rigorously proved by Hughes, Ingold, and Taher (*J.*, 1940, 949), and its effect on the free energies of normal molecules was finally established by Baker and

Hemming (*J.*, 1942, 191).* Although the effect was correctly associated by Baker specifically with the presence of CH-bonds, H—C—C=C, Hughes, Ingold, Masterman, and MacNulty pointed out (*J.*, 1940, 909) that a comparable energy effect arises even when quaternary carbon is attached to an ethenoid system; this is because of the reduction of electronic zero-point energy, which can result from the concentration of *CC*-electrons in the direction of the unsaturated centre. For our purposes it is convenient to include this effect in the hyperconjugation energy associated with the attachment of alkyl groups to ethenoid carbon. Looking back we can identify this hyperconjugation energy, at least roughly, with some of the differences observed by Kistiakowsky, Ruhoff, Smith, and Vaughan in the heats of hydrogenation of simple olefins (*J. Amer. Chem. Soc.*, 1935, **57**, 876). Even for one particular alkyl group, such as methyl, the effect on hydrogenation heat was found to be largely constitutive, but the range $1{\cdot}5 \pm 1$ kilocal. for the methyl group covers the data.

In the system (R = H or CH_3)

$$(CH_3)_2C{:}CR{\cdot}CH_2Br \rightleftharpoons (CH_3)_2CBr{\cdot}CR{:}CH_2$$

the equilibrium proportion of the αα-dimethylallyl isomeride is too small for experimental detection (Claisen, *loc. cit.*). Taking 3 kilocals. as the order of the contribution made by the hyperconjugation of the *gem*-methyl groups to the free energy difference, and disregarding other influences, we find the equilibrium proportion of the αα-dimethylallyl compound at 300° K. should be of the order of 1%. The system

$$CH_3{\cdot}CH{:}CH{\cdot}CH_2Br \rightleftharpoons CH_3{\cdot}CHBr{\cdot}CH{:}CH_2$$

provides a better check on the assumed energy effects, inasmuch as the equilibrium ratio is measurable and known (Winstein and Young, *J. Amer. Chem. Soc.*, 1936, **58**, 104). Taking 1·5 kilocals. as the free energy difference contributed by the hyperconjugated methyl group, and neglecting other factors, we calculate that at 293° K. the equilibrium ratio, γ- to α-methylallyl, should be 93% : 7%, and at 373° K. it should be 88% : 12%. The figures are accidentally in better agreement with the observational values, 87% : 13% at 293° K., and 85% : 15% at 373° K., than would have been expected in view of the uncertainty in the energy difference. The general principles here illustrated may, of course, be quite extensively applied.

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4. *The Modes of Addition to Conjugated Unsaturated Systems. Part IX. A Discussion of Mechanism and Equilibrium, with a Note on Three-carbon Prototropy.*

By P. B. D. DE LA MARE, E. D. HUGHES, and C. K. INGOLD.

The discussion given in the preceding paper, particularly of the kinetic and thermodynamic control of anionotropic rearrangement, and of the significance of conjugation and hyperconjugation energy in anionotropic equilibria, is supplemented by an analogous discussion of prototropic rearrangements in three-carbon systems, and of their equilibria; and the whole of this theory is applied in a consideration of the modes of addition of both electrophilic and nucleophilic addenda to conjugated unsaturated systems. New forms of hyperconjugation in normal molecules are recognised.

THE theory of Organic Chemistry has greatly advanced since 1928, when Part I of this series was written, which mapped the field of the succeeding experimental researches (Parts II—VIII). The subject of additions to conjugated polyenes can therefore advantageously be again reviewed. First, though it is a formal matter, we modernise the originally given classification of addenda, commencing with the explanation that we shall deal here only with heterolytic addition reactions, though sufficient concerning homolytic addition is now known (thanks largely to Kharasch) to encourage an attempt to treat that part of the subject more comprehensively

* A good review of the subject of hyperconjugation is now available (Deasy, *Chem. Reviews*, 1945, **36**, 145).

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than hitherto. We shall here consider, however, only the following classes of heterolytic addenda:

Electrophilic Addenda:

(1) Hydrogen halide type (includes ROH_2^+, *i.e.*, water or alcohol adding under acid catalysis; includes also NOCl).

(2) Halogen type.

Nucleophilic Addenda:

(3) Hydrogen cyanide type (includes malonic esters and Michael addenda generally; also water or alcohol adding under alkaline catalysis).

(4) Hydrogen type.

The fundamental change in our attitude is that, whereas, when Part I was written, so little was known of the constitutional factors of molecular energy that the discussion of orientation had to be based on inescapably qualitative considerations concerning structural effects in the relative rates of alternative reactions, now that conjugation and hyperconjugation are recognised as sources of energy contributions, which can sometimes be independently estimated, it is possible to re-express the matter in terms of the relative energies of alternative products, and thus in terms suitable to later quantitative development. When it is necessary to discuss the kinetic, as distinct from the thermodynamic, control of orientation, we can preserve the same point of view by discussing structural effects on the energies of transition states, even though one is in this case further from the possibility of quantitative treatment.

(a) *Addition of Hydrogen Halides.*—Burton and Ingold sought to show (Part I, *J.*, 1928, 910), and their arguments have been generally accepted, that the addition of hydrogen halides to olefins in solution is normally a two-stage process, which is initiated by the donation of a proton to the olefin by the electrophilic hydrogen halide molecule, and is completed by the neutralisation of the formed carbonium ion through the uptake of a halide ion. In additions to a conjugated polyene the intermediate carbonium ion is, of course, mesomeric, having therefore two or more possible positions for neutralisation in the final stage of the addition.

The initial proton uptake must occur at an end of the conjugated system of a polyene, this being the position in which the greatest negative polarisation can be developed in the transition state of the reaction. If the two ends of such a system are rendered non-equivalent by aryl or alkyl substitution, that end will be preferred as the point of initiation which is also an end of a conjugated or hyperconjugated system involving the substituent. If on account of poly-substitution two non-equivalent ends both fall within this definition, the conjugated or hyper-conjugated system involving the most polarisable substituent will control the point of attack. Thus initiation (*) occurs at C_α in β-methylbutadiene and at C_δ in α-phenylbutadiene and α-phenyl-β-methylbutadiene:

$$\overset{*}{C}H_2{:}CMe{\cdot}CH{:}CH_2 \qquad CHPh{:}CH{\cdot}CH{:}\overset{*}{C}H_2 \qquad CHPh{:}CMe{\cdot}CH{:}\overset{*}{C}H_2$$

Supposing the ions of an anionotropic system to have been formed in the initial reaction stage, it remains to consider their union to give the alternative addition products. At the outset this union must be kinetically controlled. Too little is known concerning transition states of ionisation to permit of any very specific predictions concerning the relative rates of production of the isomeric molecules from these pre-formed ions. However, two general statements may be made. One is that the thermodynamically less stable isomeride should be first formed in more than its equilibrium proportion. This is our general experience with anionotropic systems (preceding paper, p. 11), and it is to some extent made plausible by the consideration that a predisposition must exist for the free energy difference between the isomeric molecules to become reduced in the corresponding transition states of their ionisation, these states being stages on the way to the same pair of ions. The other statement is that the kinetically determined proportions of isomerides are likely to be more sensitive to solvent influence than are their equilibrium proportions. This follows from the expected greater solvation energy of the quasi-ionic transition states, than of the fully formed neutral molecules. Even when we cannot make a comparison of the kinetic and thermodynamic solvent influence, we may still expect great sensitivity to solvent influence in the cases in which the proportions of isomerides are kinetically determined. These principles apply, of course, not only to additions of hydrogen halides but also to those of halogens, and illustrations will be given in relation to both these kinds of addition.

We commence with the least mobile anionotropic systems in order to isolate the effect of kinetic control. Anionotropic chlorides are always less mobile than corresponding bromides. Butadiene itself will produce less mobile systems by addition than any alkyl- or aryl-substituted butadiene or higher polyene. Three hydrochlorides of butadiene can be formulated, but one is theoretically excluded by the principle of terminal initiation; the other two are γ-methylallyl (crotyl) chloride, $CH_3{\cdot}CH{:}CH{\cdot}CH_2Cl$ (the α-hydro-δ-chloride), and α-methylallyl chloride, $CH_3{\cdot}CHCl{\cdot}CH{:}CH_2$ (the α-hydro-β-chloride). The addition has been investigated by Kharasch, Kritchevsky, and Mayo (*J. Org. Chem.*, 1937, **2**, 489), who failed to detect the presence of any product other than these two. The proportion of γ-methylallyl chloride formed was 20—25%. This proportion was independent of the temperature between −80° and +25°, and the isolated chlorides underwent no measurable conversion under the conditions of their formation. However, prolonged treatment with hydrogen chloride at the upper end of the temperature range caused conversion finally into an equilibrium mixture containing about 75% of γ-methylallyl chloride. Obviously the thermodynamically less stable α-methylallyl chloride is first produced in much more than its equilibrium proportion.

With hydrogen bromide as the addendum a more mobile anionotropic system is produced. The same authors obtained the kinetically controlled mixture of products, containing 20% of γ-methylallyl bromide, only at low temperatures, and with the careful exclusion of oxidant catalysts. At higher temperatures, and especially in the presence of such catalysts, much larger proportions of γ-methylallyl bromide were obtained; and, consistently, in these conditions the isolated bromides underwent facile interconversion to produce the equilibrium mixture, which, according to Winstein and Young's determination (*J. Amer. Chem. Soc.*, 1936, **58**, 104), contains 87% of γ-methylallyl bromide at 25°. Equilibrium proportions of the order of those found for chlorides and bromides are, as we have seen, consistent with the principles outlined in the preceding paper.

An interesting variant of these phenomena arises in the case of vinylacetylene. Carothers, Berchet, and Collins have shown (*J. Amer. Chem. Soc.*, 1932, **54**, 4066) that the initial product of addition of hydrogen chloride contains a large proportion of chloromethylallene, $CH_2{:}C{:}CH{\cdot}CH_2Cl$ (an α-hydro-δ-chloride with the added hydrogen at the acetylene end), which in the presence of hydrogen chloride or cuprous chloride rearranges completely to yield chloroprene, $CH_2{:}CCl{\cdot}CH{:}CH_2$ (the corresponding α-hydro-β-chloride). Initiation only at the acetylenic end of this molecule accords with the principle (Hughes, Ingold, Masterman, and MacNulty, *J.*, 1940, 909) that in such a case the electrons will concentrate preferentially towards the *more* unsaturated end. The proportions of the tautomerides at equilibrium will be determined partly by the (negative) butadienoid resonance energy of chloroprene, probably about 6 kilocals., and partly by the (positive) " strain " energy of the chloromethylallene, probably about 8 kilocals.; obviously, therefore, chloroprene should be formed to the complete exclusion of the allene derivative. But initially the thermodynamically labile isomeride is produced in considerable proportion, consistently with the general principle given above.

For substituted butadienes the number of possible isomeric hydrohalides is three or six according as the system is symmetrical or not. Our knowledge of the effect of the phenyl group in promoting the mobility of anionotropic systems shows that in the case of phenyl-substituted butadienes there will be hardly any possibility of isolating either hydrobromides or hydrochlorides out of equilibrium. This being so, the principles governing the terminal initiation of addition, and the dominating energy effect of phenyl–vinyl conjugation, together should secure the production of a single isomeride in most cases, *e.g.*,

In the case of α-phenylbutadiene, the exclusive formation of the expected δ-hydro-γ-bromide has been established by Riiber (*Ber.*, 1911, **44**, 2977), and of the corresponding δ-hydro-γ-chloride by Muskat and Huggins (*J. Amer. Chem. Soc.*, 1934, **56**, 1239).

The methyl-substituted butadienes will produce less mobile addition products than their phenyl analogues, but we may expect that it will be difficult to isolate hydrobromides out of equilibrium, although the corresponding task with hydrochlorides should prove comparatively easy. Most of the recorded investigations relate to additions of hydrogen bromide. With β-methylbutadiene we expect α-initiation, and this must lead to the already discussed system

consisting of γγ- and αα-dimethylallyl bromides, $CH_3 \cdot CMe{:}CH \cdot CH_2B^r$ and $CH_3 \cdot CMeBr \cdot CH{:}CH_2$ (preceding paper, p. 12). Here the γγ-isomeride is much the more thermodynamically stable owing to the doubled methyl hyperconjugation; and consistently, Claisen has shown (*J. pr. Chem.*, 1922, **105**, 65; cf. Farmer and Marshall, *J.*, 1931, 139) that the product of addition of hydrogen bromide to isoprene consists exclusively of γγ-dimethylallyl bromide. Hydrogen chloride has been shown to add in the same way (Jones and Chorley, *J.*, 1946, 832). βγ-Dimethylbutadiene is a closely similar example since the extra methyl group has a like effect on both isomerides, $CH_3 \cdot CMe{:}CMe \cdot CH_2Br$ and $CH_3 \cdot CMeBr \cdot CMe{:}CH_2$, of the formed anionotropic system; and correspondingly, Claisen and Farmer and Marshall have established (*locc. cit.*) that the sole product of the addition of hydrogen bromide to this hydrocarbon is βγγ-trimethylallyl bromide (*loc. cit.*).

A less black-and-white picture is presented by αδ-dimethylbutadiene. In this case the same authors proved that both the isomerides which are rendered possible by the terminal initiation of addition are obtained in the proportions here indicated:

(~90%) $CH_3 \cdot CH_2 \cdot CHBr \cdot CH{:}CH \cdot CH_3$ $CH_3 \cdot CH_2 \cdot CH{:}CH \cdot CHBr \cdot CH_3$ (~10%)

Assuming equilibrium, the preponderance of an α-hydro-β-bromide is to be expected, because we have to balance the energy effects of hyperconjugation by methyl in the one isomeride and by ethyl in the other, and, as Baker has shown both theoretically and practically, the former effect is the greater. Taking the differential energy effect a 0·4 kilocal. (from the differences in the heats of hydrogenation of but-2-ene and pent-2-ene), the equilibrium proportions at the experimental temperature are calculated to be 70% : 30%. The agreement is more than sufficient, since in using so small an energy difference we are almost certainly making the calculation dependent on a quantity which is of the same order of magnitude as the quantities neglected.

(b) *Additions of Halogens.*—Since the date of Burton and Ingold's paper a valuable discussion of the mechanism of halogen addition to simple olefins has been given by G. Williams (*Trans. Faraday Soc.*, 1941, **37**, 749). His discussion confirms the view that the simplest mechanistic conditions arise in strongly ionising, especially in aqueous, solvents. The addition then consists of the electrophilic attack of the halogen molecule on one of the unsaturated carbon atoms, followed by a neutralisation of the formed carbonium ion through the uptake of a halide ion. Williams also draws attention, however, to the evidence, which was even at that date beginning to accumulate, largely through the work of Robertson and his collaborators, that in less ionising and non-ionising solvents halogen addition is markedly multiform. The continuing researches of Robertson have now brought to light a number of homogeneous mechanisms, quite apart from the heterogeneous processes which may occur on suitable surfaces in the presence of non-polar solvents. The kinetically distinguished homogeneous processes include (i) second-order chlorine- and bromine-addition with rate proportional to [olefin] [hal_2], (ii) third-order bromine addition (but not chlorine addition) with rate proportional to [olefin] [Br_2]^2, (iii) fourth-order bromine (but not chlorine) addition with rate proportional to [olefin] [Br_2]^3. All these reactions are shown to be electrophilic, but it is by no means certain that they all involve an intermediate having a carbonium ionic centre, though Williams has suggested that the third-order reactions may do so. It is not necessary to enumerate here the additional electrophilic mechanisms involving special homogeneous catalysts; most of these can probably be accommodated in an extension of White and Robertson's original formulation of such reactions (*J.*, 1939, 1509; cf. Williams, *loc. cit.*; Swedlund and Robertson, *J.*, 1945, 131; *J.*, 1947, 630; de la Mare, Scott, and Robertson, *J.*, 1945, 509; Waters, Caverhill, and Robertson, *J.*, 1947, 1168). All the above-mentioned mechanisms seem to us likely to play some part in the applications to conjugated systems with which we shall be concerned, though no kinetic studies of halogen addition to conjugated polyenes are yet available to support this assumption. We shall not need to refer here to the group of *nucleophilic* halogen additions, which apply to αβ-unsaturated carbonyl and nitro-compounds in conditions of hydrogen-ion catalysis (Morton and Robertson, *J.*, 1945, 129; de la Mare and Robertson, *J.*, 1945, 888; Ting and Robertson, *J.*, 1947, 628).

In additions to conjugated polyenes the precise mechanism will, of course, affect the immediate, kinetically determined ratio in which the isomeric addition products are formed, but not the ultimate, thermodynamically determined ratio. Where the mechanism involves an intermediate having a carbonium-ion centre, this will be the cation of an anionotropic system, and the kinetically controlled product ratio will depend on the relative rates of uptake of an anion in the alternative possible positions. In this case, if a phase of kinetic control can be distinguished, we may expect an initial production of more than the equilibrium proportion of

the thermodynamically less stable isomeride, and this proportion is likely to be very sensitive to the solvent. In other cases the kinetically controlled product ratio will depend on the exact mechanism in ways which cannot be predicted in detail, but may be assumed to depend closely on stereochemical considerations. The possibility is therefore not excluded that the thermodynamically more stable isomeride might in special cases be formed initially in more than its equilibrium proportion.

For the purpose of considering the thermodynamic control of product proportions, we shall have to take explicit account of an energy term which could be neglected in the cases previously discussed, not because its absolute value was likely to be particularly small, but because it was always balanced in the isomerides under consideration: such balancing no longer obtains in anionotropic products formed by halogen addition. We refer to the hyperconjugation energy associated with the system $C{=}\overset{\curvearrowright}{C}{-}\overset{\curvearrowright}{C}{-}Hal$, a sort of counterpart of the hyperconjugation energy which Baker and Nathan recognised in the system $\overset{\curvearrowleft}{C}{=}\overset{\curvearrowleft}{C}{-}H$. We think that a third type of hyperconjugation, *viz.*, that of the system $H{-}\overset{\curvearrowright}{C}{-}\overset{\curvearrowright}{C}{-}Hal$, is also of energetic importance for normal molecules. Some evidence for this seems recognisable in the data of Conn, Kistiakowsky, and Smith for the heats of addition of bromine to simple olefins (*J. Amer. Chem. Soc.*, 1938, **60**, 2764).

We may expect that amongst the least mobile anionotropic systems that can be produced by the addition of halogens to polyenes will be those which are derived from butadiene itself, and that the dichloride of butadiene will be less mobile than the dibromide. The addition of chlorine to butadiene has been investigated by Muskat and Northrop (*J. Amer. Chem. Soc.*, 1930, **52**, 4043), who found the αβ-dichloride to preponderate over the αδ-isomeride in the ratio of about 2 : 1. The dichlorides underwent no interconversion under the conditions of their formation; and, indeed, the authors failed to interconvert them, although this could, no doubt, be accomplished by the aid of appropriate solvents or catalysts. We must regard the proportions as kinetically determined, since we should expect the αδ-isomeride to be the principal constituent of the mixture at equilibrium. The addition of bromine to butadiene has been investigated by several authors, but most thoroughly by Farmer, Lawrence, and Thorpe (*J.*, 1928, 729), who, in a series of solvents ranging from hexane to acetic acid, obtained dibromide mixtures containing from 38% to 70% of the αδ-isomeride. Some interconversion of isomerides in the sense αβ ⟶ αδ could be detected in the conditions of the addition, but such isomerisation was too slow to be made responsible for the formation of more than a very small proportion of the αδ-compound produced by addition. Conversion of the isolated isomerides into an equilibrium mixture was effected, and the mixture then contained about 80% of the αδ-dibromide, a figure which Muskat and Northrop have confirmed. These results illustrate both the sensitivity of the kinetically-controlled product ratio to solvent influences, and the initial production of an excessive proportion of the thermodynamically less stable isomeride. We attribute the greater thermodynamic stability of the αδ-compound mainly to the circumstance that the energy effect of its doubled bromine hyperconjugation is greater than that of the single hyperconjugation of the same kind in the αβ-isomeride:

$$(80\%)\quad CH_2Br{\cdot}CH{:}CH{\cdot}CH_2Br \rightleftharpoons CH_2Br{\cdot}CHBr{\cdot}CH{:}CH_2 \quad (20\%)$$

The only other known cases in which a phase of kinetic control has been detected as a precursor to the formation of products in equilibrium are those of *cyclo*pentadiene and *cyclo*hexadiene, from which mixtures containing 1 : 2-dibromides are first formed, although in the readily attained equilibria the main product is the 1 : 4-compound (see below).

With phenyl-substituted butadienes we may expect to obtain only equilibrium products in additions of either bromine or chlorine. This being so, the principle of terminal initiation, and the dominating energy effect of phenyl–vinyl conjugation, will in most cases determine the exclusive formation of a single addition product. Thus α-phenylbutadiene should yield a γδ-dihalide, β-phenylbutadiene an αδ-dihalide, and αδ-diphenylbutadiene an αβ-dihalide:

$$CHPh{:}CH{\cdot}CHX{\cdot}CH_2X \qquad CH_2X{\cdot}CPh{:}CH{\cdot}CH_2X \qquad CHPhX{\cdot}CHX{\cdot}CH{:}CHPh$$

Muskat and Northrop (*loc. cit.*) have experimentally established the exclusive formation from α-phenylbutadiene of the γδ-dichloride, and Straus that of the γδ-dibromide (*Ber.*, 1909, **42**, 2867). Straus has also shown that αδ-diphenylbutadiene forms only the αβ-dibromide. The rule is that phenyl–vinyl conjugation will always be preserved to the greatest possible extent. A closely analogous case is that of hexatriene, in which a dominating tendency to the preservation

of butadienoid conjugation should determine αβ- and αζ-addition to the exclusion of αδ- and γδ-addition. The addition of bromine to hexatriene has been investigated by Farmer, Laroia, Switz, and Thorpe (*J.*, 1927, 2937), who were able to isolate only the αβ- and αζ-dibromides $CH_2Br{\cdot}CHBr{\cdot}CH{:}CH{\cdot}CH{:}CH_2$ and $CH_2Br{\cdot}CH{:}CH{\cdot}CH{:}CH{\cdot}CH_2Br$.

In β- and γ-alkylated butadienes we see the tendencies already illustrated with respect to butadiene reinforced by alkyl hyperconjugation; and, since the thermodynamically less stable addition compound is necessarily a tertiary halide, we may expect only equilibrium products in the addition of bromine; they would probably be difficult to avoid in the addition of chlorine under ordinary conditions. Thus in β-methylbutadiene the initiation of addition at C_α excludes γδ-addition, and of the remaining possible addition products only the αδ-compound, $CH_2X{\cdot}CMe{:}CH{\cdot}CH_2X$, preserves the hyperconjugation of the methyl group. Since halogen hyperconjugation works in the same direction, we may be sure that the αδ-dihalides will preponderate at equilibrium. Jones and Williams have shown (*J.*, 1934, 829) that the dichloride obtained from isoprene consists essentially of the αδ-compound, although indications were obtained of the formation of a second isomeride in small amount. The dibromide of isoprene has also been shown to consist essentially of the αδ-compound (Bergmann, *J. Russ. Phys. Chem. Soc.*, 1898, **30**, 1885; Staudinger, Muntwyler, and Kupfer, *Helv. Chim. Acta*, 1922, **5**, 756). The case of βγ-dimethylbutadiene is essentially similar, the extra methyl group having a like effect on the stability of each of the formed dihalides. Accordingly, it has been found that the dibromide of this hydrocarbon consists mainly of the αδ-compound, $CH_2Br{\cdot}CMe{:}CMe{\cdot}CH_2Br$ (Kondakow, *J. pr. Chem.*, 1900, **62**, 166; Macallum and Whitby, *Trans. Roy. Soc. Canada*, 1928, iii, **22**, 33; Farmer, Lawrence, and Scott, *J.*, 1930, 510; Sweeting and Johnson, *J. Amer. Chem. Soc.*, 1946, **68**, 1057). αγ-Dimethylbutadiene is another case in which an equilibrium product should be readily formed. Here the initiation of reaction at C_β excludes the αβ-dihalide, and, as regards the remaining possibilities, the effect of methyl hyperconjugation should be roughly balanced (although the methyl groups are not strictly equivalent), whilst halogen hyperconjugation should favour the αδ-isomeride. The addition of bromine has been investigated, and the αδ-dibromide, $CHMeBr{\cdot}CH{:}CMe{\cdot}CH_2Br$, has been proved to be the principal product (Farmer, Lawrence, and Scott, *loc. cit.*).

Three terminally dialkylated butadienes have been studied with respect to the mode of addition of bromine, namely αδ-dimethylbutadiene (Duden and Lemme, *Ber.*, 1902, **35**, 1338; Farmer, Lawrence, and Scott, *loc. cit.*), *cyclo*pentadiene (Thiele, *Annalen*, 1900, **314**, 296; Farmer and Scott, *J.*, 1929, 172), and *cyclo*hexa-1 : 3-diene (Farmer and Scott, *loc. cit.*). In these cases the anionotropic systems formed by addition are expected to be somewhat less mobile than those considered in the preceding paragraph. In the examples of *cyclo*pentadiene and *cyclo*hexa-1 : 3-diene the formation of mixtures of dibromides which are distinctly out of equilibrium has been observed by Farmer and his collaborators. In all three cases the equilibrium product consists essentially of the 1 : 4-dibromide. The prediction of these equilibria is at present impossible, since it involves the setting-off of the effect of methyl or methylene hyperconjugation in the 1 : 2-dihalide against that of an extra halogen hyperconjugation in the 1 : 4-isomeride, and we have no independent data by which these effects can be weighted relatively to each other. On general grounds it seems probable that the energy effect of halogen hyperconjugation will be rather strongly dependent on whether the halogen is in primary, secondary, or tertiary combination.

(c) *Note on Three-carbon Prototropy.*—Just as the preceding consideration of the behaviour of electrophilic addenda towards conjugated systems required reference to the theory of anionotropic systems, so the discussion still to be given of nucleophilic addenda will involve reference to the chemistry of prototropic systems. As we are not submitting a paper on prototropy at the present time, it is needful to include here some remarks on those aspects of the subject which we shall require for application in the last sections of this paper.

One such aspect relates to so-called " three-carbon " systems in equilibrium. These systems are propenes carrying at least one unsaturated end-group of " activating " character, such as COR, CO_2R, COCl, CO_2^-, or CN. Most of the data for the equilibria of these systems we owe to Kon and Linstead. These data were once collated and discussed by one of the present authors (*Ann. Reports*, 1927, **24**, 109—113; cf. *ibid.*, 1928, **25**, 119), but this was before conjugation and hyperconjugation energy were recognised, and the correlation could not, therefore, be put upon the basis of energy relations; which is not only the right basis for future development, but is also the best one for present application. We therefore here present the matter in a revised form : what we shall say is in part a translation, in part a correction, of the older discussion.

The observations may be grouped as follows. In three-carbon systems with a single activating group, the equilibrium between the αβ- and the βγ-unsaturated forms is not particularly sensitive to the nature of the activating group, but is highly sensitive to substitution in certain positions in the three-carbon system itself. Whenever the γ-position (*every* γ-position if there is more than one) is unsubstituted, as in crotonic, ββ-dimethylacrylic, or β-methylcinnamic acids (I; R = H, Me, Ph)—many other examples could be given—the form exclusively present at equilibrium is the αβ-unsaturated form. As the mentioned examples show, the replacement of β-hydrogen by β-methyl, or even by β-phenyl, makes no difference to this result. However, the introduction of a single γ-methyl group shifts the balanced reaction towards the side of the βγ-unsaturated isomeride, which now becomes always an important, and often the preponderating form at equilibrium (II). A γ-phenyl group has a larger effect in the same direction (Bougeault), the βγ-isomeride being now the exclusive form at equilibrium (III) :

$CH_3 \cdot CR{:}CH \cdot CO_2H$	$CH_3 \cdot CH_2 \cdot CR{:}CH \cdot CO_2H$	$C_6H_5 \cdot CH_2 \cdot CH{:}CH \cdot CO_2H$
⇅	⇅	⇅
$CH_2{:}CR \cdot CH_2 \cdot CO_2H$	$CH_3 \cdot CH{:}CR \cdot CH_2 \cdot CO_2H$	$C_6H_5 \cdot CH{:}CH \cdot CH_2 \cdot CO_2H$
(I.)	(II.)	(III.)

On the other hand, higher γ-alkyl groups are less effective than γ-methyl as is shown by the following results (Kon and May) relating to the acids $(R \cdot CH_2)_2C{:}CH \cdot CO_2H$ and their isomerides (IV; R = H, Me, Et, Pr^{β}) :

γ-Substituent (R)	H	CH_3	$CH_2 \cdot CH_3$	$CH(CH_3)_2$
βγ-Form at equilibrium	0%	95%	67%	51%

Finally, there is evidence that, just as γ-methyl groups shift equilibria so as to favour the βγ-unsaturated forms, so α-methyl substituents shift them in the opposite direction, as is illustrated (Goldberg and Linstead) by the pentenoic acids and their methyl derivatives,

$$CH_3 \cdot CHR \cdot CH{:}CR' \cdot CO_2H \rightleftharpoons CH_3 \cdot CR{:}CH \cdot CHR' \cdot CO_2H$$

V; R, R′ = H, Me) :

Acids	γ-Methylpentenoic	Pentenoic	α-Methylpentenoic
βγ-Form at equilibrium.....	94·4%	24·6%	19·3%

The theory of these relationships is as follows. The non-γ-substituted compounds, such as (I), exist at equilibrium practically entirely in the αβ-form, because the (negative) conjugation energy of the olefinic bond with the activating group contributes to the free energy of this form, whilst the βγ-form possesses no compensating constitutional energy term conferred on it by the special position of its double bond. β-Substituents conjugate or hyperconjugate with the double bond in either position and therefore have only second-order effects on the energy difference which determines the equilibrium. In the γ-methyl compounds (II), the conjugation energy in the αβ-form is compensated to a considerable extent in the βγ-form by the hyperconjugation energy of the γ-methyl group with the βγ-double bond. In γ-phenyl compounds (III), there is an over-compensation in the same sense, due to the large resonance energy of phenyl-to-vinyl conjugation (this vol., p. 16). It is a characteristic of alkyl hyperconjugation (indeed, it is the property which led Baker and Nathan to discover the phenomenon) that the methyl group is more effective than ethyl, and still more than *iso*propyl, and so on: $H \ll \{Me > Et > Pr^{\beta} > Bu^{tert.}\}$. Thus we can readily understand the observed order of alkyl effects as illustrated in series (IV). Finally, it is obvious that, just as γ-methyl hyperconjugates with the βγ-double bond, so an α-methyl group will hyperconjugate with the αβ-double bond, but less strongly, because this effect competes with the conjugation between the same double bond and the activating group. Thus can be understood the data illustrated in series (V).

In addition to activated systems such as these, we shall have occasion to consider true three-carbon systems, *i.e.*, propene systems not terminated by unsaturated groups of high electron-affinity. These systems cannot dissociate into ions under the relevant experimental conditions, but we shall be concerned with their formation, irreversibly, and out of thermodynamic equilibrium, from ions which have been produced by addition. Even here, however, we shall maintain an analogous point of view by considering the effect of conjugation and hyperconjugation energy on the alternative transition states of ionic recombination, remembering that, as has already been discussed in other cases, we may generally expect to obtain more than the equilibrium amount of the thermodynamically less stable isomeride.

(d) *Addenda of the Hydrogen Cyanide Type.*—The reactions of these addenda are all base-catalysed, with the main activation barrier in the first stage; which consists of the addition of a nucleophilic anion, such as OMe^-, CN^-, $CH(CO_2Me)_2^-$, etc., to a positively polarisable position in a conjugated system terminated by at least one unsaturated, electron-attracting group, such as COR, CO_2R, CN, etc. The addition is strongly reversible: often, under the conditions of preparative work, the rates of formation of the addition product, and of its dissociation into its factors, are of quite the same order of magnitude. In additions to butadiene derivatives the β- and δ-positions with respect to the activating group are both positively polarisable, and we shall be largely concerned with the question of which of them receives, and succeeds in holding, the anionic addendum.

The addition product of the first stage of reaction is an anion, which in the second stage unites with a proton. Further, the product of the first stage is the anion of a prototropic system, so that there are generally alternative final products, differing in the position of a proton. However, we shall most fully discuss the first stage, which determines the carbon framework of the final addition product. The principles governing the second stage of addition are essentially those outlined in the preceding section (*c*).

There can be no doubt that if the direction of the first stage addition process were kinetically controlled, *i.e.*, if the anionic addition product could not again dissociate, the addition to a butadiene chain with an appropriate end-group would be substantially terminal; *i.e.*, the δ-position in the system would receive the adding anion. The reason is the same as that given for terminal initiation in the addition of electrophilic reagents, such as chlorine or hydrogen chloride, to butadienes: polarity in a freely conducting, linear system is necessarily developed at its ends. The difference between the two cases is that the group of nucleophilic additions now under consideration are more prone to, and have more opportunity for, reversal. However, we may venture the prediction that if, in order to exclude effects due to reversibility, we should isolate a Michael addition product, *e.g.*, of methyl malonate to methyl sorbate, $CH_3{\cdot}CH{:}CH{\cdot}CH{:}CH{\cdot}CO_2Me$, or of methyl cyanoacetate to methyl γ-methylsorbate, after an indefinitely small amount of reaction, the addition product would consist substantially of the esters formed by addition in the δ-position only. The compositions would thus be quite different from those of the products of the same reactions allowed to run to equilibrium (see below). Naturally this applies only if the conjugated system stops at the δ-position.

However, in preparative work, the additions are usually allowed to run to equilibrium, and hence, in seeking an interpretation of existing observations, it is necessary to consider the direction of addition as thermodynamically controlled, *i.e.*, as dependent solely on the relative free energies of the end-products. For the addition, *e.g.*, of malonic esters to β-vinylacrylic esters, $CH_2{:}CH{\cdot}CH{:}CH{\cdot}CO_2R$, there are two possible, prototropically related, end-products of δ-addition, and one end-product of β-addition:

$$\begin{array}{l} CH_2{\cdot}CH_2{\cdot}CH{:}CH{\cdot}CO_2R \\ \quad\quad\quad\

The observations on Michael and related additions to the phenylated derivatives of β-vinylacrylic esters are also quoted or reported in Part IV (*loc. cit.*). The presence of a phenyl group in the δ-position (without a similar group in the α- or β-positions), as in cinnamylideneacetic esters, $C_6H_5{\cdot}CH{:}CH{\cdot}CH{:}CH{\cdot}CO_2R$, leads to practically exclusive β-addition. Clearly, this mode of reaction preserves the phenyl-to-vinyl conjugation, the large resonance energy (7 kilocals.) of which may be held responsible for the direction of the addition. Michael reactions pursue the same direction even with cinnamylidenemalonic esters, $C_6H_5{\cdot}CH{:}CH{\cdot}CH{:}C(CO_2R)_2$, in which an extra α-carboxyl group is present to enhance the tendency to δ-additions. However, it was shown in Part VI (Duff and Ingold, *J.*, 1934, 87), by study of the further transformations of the adducts under the conditions of their formation, that δ-addition has an appreciable rate in this case, and that the δ-addition product can be produced if it can simultaneously be consumed, even though it has a smaller thermodynamic stability than the β-addition product.*

Farmer and Martin have examined the addition of methyl malonate to a hexatriene ester, $CH_3{\cdot}CH{:}CH{\cdot}CH{:}CH{\cdot}CH{:}CH{\cdot}CO_2Me$ (*J.*, 1930, 960). Here the malonic ester residue might add to the β-, the δ-, or the ζ-positions of the triply unsaturated ester, and in the last two cases the product might appear in more than one prototropic form. The investigators found 67% of β-addition, and between 10% and 33% of ζ-addition, whilst δ-addition, though not excluded, was not detected. (Prototropic forms were not distinguished, the first step in the analysis of the addition product being the hydrogenation of its surviving double bonds.) Theoretically, we can feel sure that no δ-addition took place, since it would break up the butadienoid conjugation completely, whereas β-addition preserves, and ζ-addition can preserve, a butadiene system (resonance energy ~3·5 kilocals.) in the product. In the β-addition product there is hyperconjugation between the terminal methyl group and the butadiene system. In one prototropic form of the ζ-addition product there is conjugation between the butadiene system and the carbomethoxyl group, whilst in the one other form which contains a butadiene system there is not; it is, however, possible that the prototropic system does not come fully into equilibrium under the mild conditions employed to effect this addition.

(e) *Hydrogenation by Dissolving Metals.*—Burton and Ingold's theory of these reductions (Part II, *J.*, 1929, 2202) appears to retain its usefulness (cf. Kuhn and Deutsch, *Ber.*, 1932, **65**, 817; Kuhn and Hoffer, *Ber.*, 1933, **66**, 1263; Ingold and Rogers, *J.*, 1935, 717), but we take the present opportunity to modernise and simplify its application to the reduction of conjugated systems.

A metal is regarded as an electron gas enclosed in potential walls, through which electrons can escape, either directly to an adsorbed cation, or to a cation through an adsorbed, conducting organic molecule, which thereby becomes reduced. The organic molecule needs an electron-accepting group, COR, CO_2R, etc. (even aryl can so act, though with more difficulty), in order to create the positively polarised position required for an adsorption which will provide a way of escape for the metallic electrons. Carbonyl or carboxyl groups may have their electron-affinity increased, by their engaging in a pre-equilibrium with an adding proton, in order to produce a sufficient positive polarisation; and the presence of a covalently or electrostatically bound proton in the electron acceptor will in any event be required to hold the electrons transferred from the metal to the reducible system. Although desorption of the latter may take place after the reception of only one electron, as in pinacol formation, it occurs more normally when two electrons have been taken up, octets have been completed, and a negative charge has been acquired by the organic group. The components ($H^+ + 2e$) of a hydride ion (H^-) have now been added in this surface reaction, which is evidently to be classified as heterolytic. After desorption, the reduction is completed homogeneously † by the addition of a proton (H^+).

In the case of a butadiene system with an electron-accepting α-group, the positive polaris-

* Malachowski, Bilbel, and Bilinski-Tarosowicz (*Ber.*, 1936, **69**, 1295) obtained a normal addition product (ethyl 1-benzylpropane-1 : 1 : 2 : 3-tetracarboxylate) from ethyl benzylmalonate and ethyl fumarate, whereas Rydon (*J.*, 1935, 420; cf. Ingold and Rydon, *J.*, 1935, 857) had obtained an abnormal product (ethyl 1-benzylpropane-1 : 2 : 3 : 3-tetracarboxylate), having a transferred carbethoxyl group, and Duff and Ingold (*loc. cit.*), before that, had obtained a product which was probably abnormal, although they had given it the normal formula. (They were interested only in its decarboxylated hydrolysis product, α-benzyltricarballylic acid.) The first-named authors seem to be unaware that, by a series of reactions (Dieckmann ring-closure and alcoholysis) first elucidated by Holden and Lapworth (*J.*, 1931, 2370), and well supported subsequently, normal and abnormal Michael addition products are generally interconvertible under the experimental conditions of Michael reactions, and that, in particular, it is commonly possible to obtain a normal product in place of an abnormal one by a suitable adjustment of conditions.

† We regard this reaction as homogeneous for lack of more intimate knowledge, but it may in some cases occur very quickly after desorption.

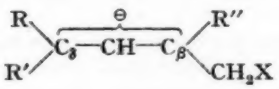
ation, and therefore the adsorption, will take place at the δ-end of the conjugated chain, for just the reason already given for the terminal initiation of the other types of addition reaction. At the desorption stage, the δ-position will be negatively charged. In some structures the charge may be held in this position by a second electron-absorbing group until combination with a proton supervenes. Thus we interpret the 1 : 4-reduction of αδ-diphenylbutadiene, cinnamylideneacetic acid, and muconic acid, and, likewise, the 1 : 6-reduction of αζ-diphenylhexatriene, and so on. In the more general case the charge wil become distributed in the desorbed mesomeric anion, so that (from butadiene compounds) 1 : 2- and 1 : 4-reduction products will be formed side by side.

In almost all cases the position taken up by the proton linked in the final stage of reaction will be kinetically, and not thermodynamically, controlled. If this were not so, butadiene-1 : 4-dicarboxylic (muconic) acid, for example, would not, by treatment with sodium amalgam, yield but-2-ene-1 : 4-dicarboxylic acid, but would give the more stable but-1-ene acid, into which the but-2-ene acid can in fact be converted by alkalis at higher temperatures than those which suffice for the reduction. This, indeed, is a case in which the equilibrium between the possible reduction products is comparatively easily set up : in most other cases, including those discussed below, the conditions of reduction will be milder by a still larger margin than those necessary to bring to equilibrium the three-carbon system involved in the final reaction-stage.

Burton and Ingold examined experimentally the proportions in which αβ- and αδ-dihydro-compounds were formed by reduction with amalgams from vinylacrylic acid, $CH_2{:}CH{\cdot}CH{:}CH{\cdot}CO_2H$, and certain methylated derivatives, in some cases using acidic as well as alkaline solutions, *i.e.*, operating with the free acids as well as with their anions. The results of these authors' analyses of the dihydro-products are summarised in the following scheme :

	αβ-Dihydro-isomeride from			
Vinylacrylic derivative	Parent	δ-Me	βδ-DiMe	ββδ-TriMe
Alkaline medium	0%	40%	28%	38%
Acidic ,, ...	18%	55%	—	—

The mesomeric anion concerned in the final reaction-stage in all these cases may be represented by the formula



where R, R′, and R″ may be either H or Me, and CH_2X may be either $CH_2{\cdot}CO_2H$ or $CH_2{\cdot}CO_2^-$. Burton and Ingold discussed the relative rates of proton combination at the β- and δ-positions on the hypothesis that the inductive effect of alkyl groups " repels " the negative charge to the more remote of the two positions. Now we realise that alkyl effects are hyperconjugative, rather than inductive, *i.e.*, that they have their origin in a quantal resonance, rather than in electrostatic forces. Hence we must put the theory on to the basis (which is equivalent in its results) that alkyl groups " attract " the double bond, *i.e.*, tend to fix it in the position permitting hyperconjugation. Here we may point out that, unlike aryl, carbonyl, or carboxyl groups, which could in principle conjugate either with the lone electrons of the anionic charge or with the π-electrons of the double bond, alkyl and substituted alkyl groups can hyperconjugate only with the double bond. The direction of the electron redistribution involved in hyperconjugation is unambiguous, $Alk\overset{\curvearrowright}{\text{—}}C\overset{\curvearrowright}{=}C$, and hence we can at once write down the series (Alk =) $CH_2{\cdot}CO_2^- > CH_3 > CH_2{\cdot}CO_2H > H$ for the relative importance of the effect in the cases summarised in the above general formula. It is to be emphasised, however, that we are not here dealing with a fully formed double bond, as in an equilibrium problem, but only with the developing double bond present in each of the alternative transition states of the final proton union. Hyperconjugation in these states, however, will undoubtedly affect the relevant activation energies, for there is plenty of indirect evidence in the behaviour of pseudo-acids (this vol., p. 11) that the formation of a prototropic system from its ions is an activated process.

With these ideas in mind the qualitative relationships shown in the preceding figures can readily be understood. In the presence of only a single hyperconjugating group, $CH_2{\cdot}CO_2^-$, the most powerful of the above series, in the β-position, proton combination takes place nearly exclusively in the δ-position. With a weaker β-group, $CH_2{\cdot}CO_2H$, or with the same β-group, $CH_2{\cdot}CO_2^-$, partly compensated by a weaker δ-group, CH_3, the want of balance is reduced but

not inverted. With the weaker β-group, $CH_2 \cdot CO_2H$, over-compensated by the stronger δ-group, CH_3, the unbalance is inverted. The effect of a δ-methyl group is seen to be partly undone by an added β-methyl group, and partly restored again by an added *extra* δ-methyl group.

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5. *The Structure of Starch. The Ratio of Non-terminal to Terminal Groups.*

By F. BROWN, T. G. HALSALL, E. L. HIRST, and J. K. N. JONES.

An assay of the proportion of terminal groups present in various starches has been made by measuring the amount of formic acid liberated on oxidation of the polysaccharide by potassium periodate. The results obtained are in good agreement with those derived by measurement of the amount of tetramethyl methylglucoside resulting from the methanolysis of the corresponding methylated starch derivatives. Few, if any, glucose residues linked solely through carbon atoms 1 and 6 can therefore be present in starch. The amylose component of certain starches has been examined and shown to contain approximately one non-reducing end-group for every 250 glucose residues. The yield of formic acid produced on oxidation of the whole starch with potassium periodate, combined with an estimate of the amylopectin content of the starch obtained iodometrically, has enabled a calculation to be made of the ratio of terminal to non-terminal groups in the amylopectin component. For many varieties of amylopectin this ratio is 20 : 1, but there are exceptions, for example, the amylopectin component of potato, sweet potato, and arrowroot starches, where the ratio is higher.

THE application to the glycogen series of Hudson and Jackson's method of oxidation of glycosides by periodic acid has been described in a previous paper (Halsall, Hirst, and Jones, *J.*, 1947, 1399). In the present communication we record results obtained in the course of work on the structural chemistry of the starches. In the first place, evidence has been sought concerning the nature of the linkages in starch. It has been established that methylglycosides of the pyranose series yield 1 mol. of formic acid on oxidation with the periodate ion, and from this it follows that in a polysaccharide molecule which has no appreciable proportion of reducing end-groups any pyranose sugar residue which is linked to other residues only through C_1 (and is therefore an end-group) or only through C_1 and C_6 (main-chain groups), will give rise to 1 mol. of formic acid. If, therefore, the proportion of end-groups determined by the methylation technique is the same as that estimated from the amount of formic acid liberated in the periodate oxidation, it is clear that the polysaccharide can contain no sugar residues linked only through C_1 and C_6. On the other hand, the excess of formic acid would give a measure of the proportion of pyranose residues linked solely through C_1 and C_6. The importance of this lies in the fact that the estimations of formic acid can be readily carried out whereas the separation and quantitative estimation of a mixture of 2 : 3 : 6-trimethyl glucose and 2 : 3 : 4-trimethyl glucose are by no means easy tasks especially when the latter sugar is present in small amount. The new method, therefore, provides a delicate test for the presence in starch and cellulose of main-chain glucose residues linked through C_1 and C_6 in place of the normal C_1 and C_4 linkages. The occurrence in starch of branched chains involving linkages at C_1, C_4, and another carbon atom, including C_6, does not involve the liberation of any additional formic acid, since no grouping of the type –CH(OH)·CH(OH)·CH(OH)– is then present in the residue concerned. In the course of the present experiments many duplicate series of end-group determinations have been performed by both the methylation method and the periodate method, and in no case has any significant discrepancy been observed between the two sets of values. It follows, therefore, that in these starches there can be no appreciable occurrence of glucose residues linked only through C_1 and C_6.

Another problem which has been investigated is concerned with the size of the repeating unit in the amylopectin portion of the various starches. Information about this is required in order to decide whether or not the amylopectins of different starches possess the same type of structure, and whether samples of the same starch, differing in maturity or in respect of the botanical variety of the plant from which it was derived, have similar proportions of end group. The average size of the repeating units in some amylopectins can be estimated directly, both by the methylation technique and by the periodate method. These include waxy maize starch, which contains a negligible proportion of the amylose component, and amylopectins which have been isolated from the starch granule and separated from the amylose component by one of the

processes recently devised for this purpose (see, for example, Schoch, "Advances in Carbohydrate Chemistry", 1945, **1**, 347; Baldwin, *J. Amer. Chem. Soc.*, 1930, **52**, 2907; Whistler and Hilbert, *ibid.*, 1945, **67**, 1161; Haworth, Peat, and Sagrott, *Nature*, 1946, **157**, 19; Higginbotham and Morrison, *Chem. and Ind.*, 1947, 45). Unfortunately, the separation of pure amylopectin is at best a lengthy and difficult process, and we record results in this paper only for one such purified amylopectin, which was very kindly put at our disposal by Mr. R. S. Higginbotham of the British Cotton Industry Research Association. Estimates of the average sizes of the repeating units of other amylopectins were arrived at indirectly by the following method. First, the relative proportions of amylose and amylopectin present in whole starch were estimated by the iodine-binding power method of Bates, Rundle, and French (*J. Amer. Chem. Soc.*, 1943, **65**, 142). The proportion of end-group in the whole starch was then determined by periodate titration. The amount of formic acid liberated by the long unbranched molecule of amylose, even after allowing for oxidation at a possible reducing end-group, is small in comparison with that given by the numerous end-groups in amylopectin, and to a first approximation it may be neglected. It is possible, therefore, to calculate the proportion of end-groups present in the amylopectin component. A similar calculation can be made using the figure for the proportion of end-groups estimated by the methylation method. In this case the influence of the amylose content of the whole starch on the final result is still less, and it is significant that the end-group figures for amylopectins so obtained agree within the limits of experimental error with those derived from the periodate oxidation experiments.

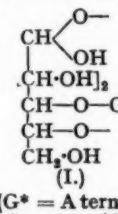
Source of starch.	Amylose content, %.	Wt. of starch oxidised, mg.	Yield of formic acid, mg.	Average no. of glucose residues per non-reducing end-group: (*a*) By periodate.	(*b*) By methylation.	Calc. no. of glucose residues per non-reducing end-group in the amylopectin fraction.
			Starches.			
1. Arrowroot	20	497	4·6	31	—	25
2. Banana	21	494	5·2	27	26 [1]	21
3. Maize	23	491	5·6	25	—	20
4. Pearl manioc ...	16	1002	11·9	24	—	20
5. Potato	18	1003	9·1	31	25, 28	24—26
6. Rice (I)	14	529	6·5	23	—	20
7. Rice (II)	15	485·5	6·0	24	25, 28	21
8. Rice (III) [2, 3] ...	—	—	—	—	30 [2]	—
9. Sago	26	1004	11·9	24	—	18
10. Sweet potato ...	18	512	4·5	32	28, 34	26
11. Tapioca	19	988	11·2	25	—	20
12. Wheat	19	1036	11·3	26	—	21
			Amylopectins.			
13. Waxy maize starch	0—1	1036	14·7	20	18	20
14. Potato amylopectin	0—1	514·5	6·1	24	—	24
			Amyloses.			
15. Sago amylose ...	100	—	—	—	250±100	—
16. Potato amylose (I)	90	2544	7·2	500±100 (for amylose component)	—	—
17. Potato amylose (II)	80	—	—	—	200±100 (for amylose component)	—

Samples 1, 3, 4, 5, 7, 9, 11, and 12 were commercial samples kindly supplied by Messrs. Elliott & Crabtree Ltd., Manchester.
Sample 2 was prepared by Hawkins, Jones, and Young (*J.*, 1940, 390).
Samples 6 and 8 were commercial samples from British Drug Houses Ltd.
Sample 10 was a commercial sample kindly supplied by The Laurel Starch Plant, Laurel, Miss., U.S.A.
Samples 14 and 15 were kindly supplied by Mr. R. S. Higginbotham of the British Cotton Industry Research Association.
Sample 16 was kindly supplied by Dr. Peat of Birmingham University and was separated by the "thymol" method (Haworth, Peat, and Sagrott, *Nature*, 1946, **157**, 19).
Sample 17 was prepared by the *n*-butanol–*iso*amyl alcohol precipitation method of Schoch.

[1] Hawkins, Jones, and Young (*J.*, 1940, 390).
[2] Hirst and Young (*J.*, 1939, 1471).
[3] Bell (*J.*, 1946, 476) has found one non-reducing end-group per 26—28 glucose residues in a sample of methylated rice starch.

The results are collected in the Table, from which it is evident that the amylopectin component of several starches has a repeating unit of average chain-length of 20 glucose residues. The evidence as it stands, however, does not warrant generalisations regarding amylopectins from different sources. It will be seen that some of the starches examined gave rather higher figures for the average size of the repeating unit of their amylopectin component, and it is unlikely that the discrepancies can be attributed entirely to experimental error. Included amongst these are the amylopectins from arrowroot (25 units), potato (24—26), and sweet potato (26). Furthermore, a highly purified sample of potato amylopectin prepared by Mr. R. S. Higginbotham gave directly, by the periodate method, a value of 24 units. Rice starch presents a further problem. We have examined two separate samples by both methods of assay and find for the whole starch 23—24 glucose residues (cf. Bell, *J.*, 1944, 473) per end-group, giving for the amylopectin component a value of 20 residues per end-group. On the other hand, another sample which we had examined previously (Hirst and Young, *J.*, 1939, 1471) gave for the whole starch 30—32 residues per end-group. In view of the divergence we re-investigated the original sample of the methylated derivatives of this starch and confirmed the earlier results (30—32). It is possible, therefore, that starches may vary from sample to sample in respect of either the proportions of amylose and amylopectin or the actual size of the repeating units, or both, the variation being dependent upon the maturity or the precise botanical origin of the starch. This introduces a serious additional problem into starch chemistry, some insight into which we are attempting to gain by experiments carried out in collaboration with Dr. F. W. Sansome of the Horticultural Research Station of Manchester University. The exact nature of the relationship in the starch granule of the amylose and amylopectin components is not yet clear, and the possibility cannot be ruled out that forms intermediate between the two may exist. Nevertheless, it is clear that all starches which have been examined up to the present give values within the range of 20—26 glucose residues per end-group for their amylopectin components. The gap is not a wide one, and further experiments may be expected to reveal whether or not this implies the occurrence of a variety of amylopectins in Nature.

The present results show also that the methylation method and the periodate method yield end-group values substantially in agreement with one another and thus rule out the hemi-acetal type of linkages proposed by Pacsu and Hiller (*Text. Res. J.*, 1946, **16**, 243) in their novel formulæ for starch and cellulose. Pacsu and Hiller's structure involves essentially long chains of 1 : 4-linked α-glucopyranose residues joined together by groups of the type shown diagrammatically in (I), the number of these being such that the end-group proportions as determined by the methylation process can be accommodated. The structure, however, provides additional points of attack for periodate ions, and additional quantities of formic acid would be liberated per end-group. The detailed formula pictured by these authors would, indeed, necessitate a yield of formic acid 100% or more greater than that required by a structure of the laminated type, yet in our experiments we have invariably found agreement between the end-group values estimated by the two methods. For these and other reasons which have been briefly indicated elsewhere (Halsall, Hirst, and Jones, *Nature*, 1947, **159**, 97) we regard it as very unlikely that hemi-acetal linkages of this type find any appreciable place in the structure of starch.



(I.)

(G* = A terminal glucose residue.)

The experimental error in the values given above for the average size of the repeating unit of the amylopectins is of the order ± 2 glucose residues, and the figure is not materially affected by the presence of some amylose, for which suitable correction can easily be made. It is much more difficult, however, to assess accurately the proportion of end-groups in amylose itself. In the first place, the very small proportion of end-group in the molecule renders exact analyses difficult by any method, but the uncertainties are much increased if corrections have to be made for amylopectin present as impurity, since in this case a very small proportion of amylopectin provides end-groups equal in amount to those in the amylose. Even when the proportions of amylose and amylopectin in the sample are known accurately—no easy matter in itself—assay by the methylation process would be liable to error should the preparation and purification of the methylated derivative involve even a slight change in the relative proportions of the two components. The periodate method avoids the last difficulty but has others of its own. It is not known with certainty whether or not the amylose molecule possesses a reducing end-group in addition to the non-reducing end-group, and when working with a highly purified amylose from sago we met an unexpected difficulty in that we failed to dissolve the amylose in the periodate solution, presumably owing to retrogradation of the polysaccharide. For these reasons the figures now given can be regarded only as approximate, but they do nevertheless

show that the molecular size of amylose is large, probably involving some hundreds of glucose residues. Similar high figures have been recorded previously by Haworth, Heath, and Peat (*J.*, 1942, 55), by Myrbäck (*J. pr. Chem.*, 1943, **162**, 29) and by Hassid, Cori, and McCready (*J. Biol. Chem.*, 1943, **148**, 89) for synthetic amylose prepared by Hanes's method, and for potato amylose and the amylose from maize starch (Meyer, Westheim, and Bernfeld, *Helv. Chim. Acta*, 1941, **24**, 378). A direct determination of the tetramethyl glucose obtained on hydrolysis of the methylated derivative of a specially pure (99%) sample of sago amylose, prepared by Mr. R. S. Higginbotham, indicated a chain length of 200 (± 100) glucose residues. Another sample of amylose was prepared by Schoch's method from potato starch (*J. Amer. Chem. Soc.*, 1942, **64**, 2954). This contained some 20% of amylopectin as estimated by the iodine-binding power (Bates, Rundle, and French, *loc. cit.*). It dispersed more readily in water, and the amount of tetramethyl glucose liberated on hydrolysis of the methylated derivative indicated a chain length of 250 (± 100) glucose residues. Approximately the same figure was obtained by the periodate method for a sample of potato amylose prepared by the thymol process of Haworth, Peat, and Sagrott, to whom we are indebted for a gift of this material.

Experimental.

Potato Starch.—The potato starch used was a commercial sample. Iodometric titration (Bates, Rundle, and French, *loc. cit.*; Hudson, Schoch, and Wilson, *J. Amer. Chem. Soc.*, 1943, **65**, 1380) showed the presence of 18% of amylose. In the calculation of the amylose content the uptake of iodine by pure amylose was taken as 21·5 g. per 100 g. of amylose (Higginbotham and Morrison, *loc. cit.*).

Determination of percentage of non-reducing terminal glucose residues by the periodate method. (The following details are typical for all the oxidations carried out, cf. Halsall, Hirst, and Jones, *loc. cit.*)

The starch (1003 mg.) was suspended in water (90 ml.) and potassium chloride (5 g.), and a solution of sodium metaperiodate (30 ml.; 0·275M) added. (For details of purity of reagents see Halsall, Hirst, and Jones, *J.*, 1947, 1427). The mixture was shaken, and at intervals samples (20 ml., free from starch granules) were withdrawn. Excess of ethylene glycol was added and the solution titrated with 0·1N-barium hydroxide [Found, in ml. of 0·01N-barium hydroxide per 1003 mg. of starch: 19·3 (168 hours); 20·0 (192 hours); 21·3 (264 hours), and 21·9 (336 hours)]. As the titration proceeded a concentration of starch occurred in residual aqueous mixture, and corrections are therefore necessary for each of the last three titrations. These titres correspond to the formation of 9·06 mg. formic acid after 150 hours' oxidation—the time required to oxidise completely β-methylmaltoside under these conditions (see Halsall, Hirst, and Jones, *loc. cit.*). This corresponds to the presence of one non-reducing terminal residue per 31 glucose residues.

Potato starch (504 mg.) was oxidised as above. After 191 hours' oxidation the uptake of periodate was estimated by the arsenite method (Found: One glucose residue took up 1·03 mol. of periodate). Potato starch (500·5 mg.) was oxidised as above. After oxidation (191 hours) excess of ethylene glycol was added to the reaction solution which was then continuously extracted with ether. The acid extracted was equivalent to 9·80 ml. of 0·01N-sodium hydroxide. This figure agrees well with that obtained by direct titration after 192 hours' oxidation in the first experiment described above.

An attempt was made to determine the amount of formic acid in the neutralised ether extract by the calomel method, but the yield of calomel was only about one-third of that expected. Pirie (*Biochem. J.*, 1946, **40**, 100) in a discussion of methods for the determination of small amounts of formic acid has pointed out that the calomel method gives low results with small quantities of formic acid.

Methylated potato starch was prepared in the usual manner in an atmosphere of nitrogen (Hirst and Young, *loc. cit.*). The methylated starch (3·16 g., OMe 42·6%) was boiled with methyl-alcoholic hydrogen chloride under the usual conditions; the solution was then neutralised with N-sodium hydroxide and the glucosides were isolated in the usual manner. The tetramethyl methyl-*d*-glucoside was concentrated by a preliminary extraction of the mixed glucosides from aqueous solution with purified light petroleum (b. p. 40—60°). The resulting syrup was dissolved in purified light petroleum (b. p. 60—80°) and chromatographed on active alumina by the method of Brown and Jones (*J.*, 1947, 1344), giving tetramethyl methyl-*d*-glucoside (150 mg., $n_D^{16°}$ 1·4440). This yield of end-group corresponds to one non-reducing terminal residue per 28 glucose residues (assuming a recovery of 93% of " end-group ").

In a second experiment the methylated starch (0·864 g., OMe, 42·6%) was converted into a mixture of glucosides by boiling with methyl-alcoholic hydrogen chloride. The solution was neutralised with diazomethane and immediately concentrated under reduced pressure to the syrupy mixture of glucosides. This material was dissolved in water (50 ml.) and extracted continuously with purified light petroleum (b. p. *ca.* 40°) in the usual manner {Found: tetramethyl methyl-*d*-glucoside, 38 mg., $n_D^{16°}$ 1·4430, $[\alpha]_D^{20°}$ + 39° (in water), OMe, 61·2%}. This yield corresponds to one non-terminal reducing per 28 glucose residues.

Potato Amylose.—A sample of potato amylose (amylopectin content 20%) prepared by the butanol method of Schoch from the potato starch used for methylation and oxidative studies was methylated and the product isolated in the usual manner (yield 80%). It was assumed that during the methylation the proportions of amylose and amylopectin did not alter owing to preferential experimental loss of one component.

The methylated derivative (4·0 g., OMe, 44%) was converted into the methylglucosides by boiling it under reflux with methyl-alcoholic hydrogen chloride. The resultant mixed glucosides were separated by extraction and counter-extraction with light petroleum (b. p. 40—60°) (Found: tetramethyl methyl-*d*-glucoside, 66 mg., $n_D^{16°}$ 1·4443, $[\alpha]_D^{20°}$ + 79°, OMe, 61%). This material on hydrolysis with 2N-hydrochloric acid gave crystalline 2 : 3 : 4 : 6-tetramethyl *d*-glucose.

If it is assumed that the amylopectin fraction (20%) of the polysaccharide mixture has an average repeating unit of 24 glucose residues, it can be calculated that the amylose component contains one non-reducing terminal residue per 200 ± 100 glucose residues.

A second sample of potato amylose separated from a different sample of potato starch by the thymol method by Haworth, Peat, and Sagrott (*Nature*, **1946**, **157**, 19) (amylose content 90%) on oxidation with aqueous potassium periodate solution gave a yield of formic acid corresponding to the presence of one non-reducing terminal residue per 500 ± 100 glucose residues after allowing for formic acid produced by the amylopectin fraction (10%) and by the reducing end of the amylose molecule.

Rice Starch.—This was a commercial sample and contained 15% of amylose. Oxidation of the starch with potassium periodate solution under standard conditions gave a yield of formic acid corresponding to the presence of one non-reducing terminal group per 24 ± 2 glucose residues.

The starch was converted into the methylated derivative by the method of Hirst and Young (*loc. cit.*). The product was purified by extraction with boiling water and by precipitation from chloroform with ether (OMe, 44%). A portion of the methylated derivative (3·66 g.) was dissolved in methyl-alcoholic hydrogen chloride and boiled under reflux until hydrolysis was complete. The glucosides were isolated in the usual manner and the fully methylated derivative was concentrated by extraction from aqueous solution with light petroleum (b. p. 40—60°). The resultant syrupy glycosides were then chromatographed on alumina (Found: tetramethyl methyl-*d*-glucoside, 174 mg., $n_D^{16°}$ 1·4440). This corresponds to the presence of one non-reducing terminal residue per 25 ± 2 glucose residues.

In a second experiment, the methylated derivative (2·03 g., OMe, 44·3%) on methanolysis gave a yield of methylglucosides (2·07 g.) which on partition extraction yielded tetramethyl methyl-*d*-glucoside {72 mg., $n_D^{16°}$ 1·4440, $[\alpha]_D^{20°}$ + 81° (in water)} corresponding to one non-reducing terminal per 28 ± 2 glucose residues.

Methylated "disaggregated" rice starch (part of Fraction 3, Hirst and Young, *J.*, 1939, 1471) (4·11 g.) was hydrolysed with boiling 1% methyl-alcoholic hydrogen chloride, and the methanolysis products isolated after neutralisation with silver carbonate. The tetramethyl methyl-*d*-glucoside was concentrated by extraction from aqueous solution with light petroleum, and the concentrate chromatographed on alumina (Found: tetramethyl methyl-*d*-glucoside, 163 mg., $n_D^{16°}$ 1·4455). This corresponds to one non-reducing terminal residue per 29 ± 2 glucose residues.

The methylated "disaggregated" starch (3·145 g.) was converted into the glucosides (3·642 g.) and the tetramethyl methyl-*d*-glucoside isolated by preferential extraction with light petroleum (b. p. 40—60°) {Found: tetramethyl methyl-*d*-glucoside, 116 mg., $n_D^{16°}$ 1·4441, $[\alpha]_D^{20°}$ + 80° (in water)}. This corresponds to one non-reducing terminal group per 33 ± 2 units. On hydrolysis with boiling 2N-hydrochloric acid the glucoside gave crystalline 2 : 3 : 4 : 6-tetramethyl *d*-glucose, m. p. 81°.

Amioca "Waxy" Maize Starch.—This work was made possible by gifts of starch from the British Cotton Industry Research Association and from Dr. Fred Smith of the University of Birmingham. This starch was coloured blue by the first drop of iodine and then red by any further addition. It contained a very small amount (*ca.* 1%) of amylose. Oxidation of the starch with potassium periodate solution under standard conditions gave formic acid corresponding to one non-reducing terminal group per 20 glucose residues.

The starch was methylated in a nitrogen atmosphere by portionwise addition of sodium hydroxide (30%) and methyl sulphate to its solution in 30% sodium hydroxide. Yield, 80% (after 4 methylations).

The methylated derivative (3·39 g., OMe, 44%) was boiled with methyl-alcoholic hydrogen chloride and the glucoside isolated in the usual manner. The tetramethyl methyl-*d*-glucoside was concentrated by extraction from water with light petroleum (b. p. 40—60°), and the concentrate chromatographed on alumina (Found: tetramethyl methyl-*d*-glucoside, 215 mg., $n_D^{16°}$ 1·4438, OMe, 61·4%). This corresponds to one non-reducing terminal group per 18 ± 2 glucose residues.

Sago Amylose.—This material was prepared by the British Cotton Industry Research Association, and potentiometric titrations indicated that it contained 99—100% of amylose (iodine-binding power 21·6). This amylose was methylated in the usual manner, and a practically quantitative yield (2·29 g.) of the methylated derivative was isolated {$[\alpha]_D^{20°}$ + 200° (in chloroform), OMe, 44%}. The properties of this substance were very similar to those of a methylated slightly degraded cellulose.

The methylated amylose (2·19 g.) was submitted to methanolysis and the resultant mixed glucosides were fractionated by extraction from water with purified light petroleum (b. p. 40—60°). Eventually, a fraction (35 mg., $n_D^{16°}$ 1·4531) was isolated. This fraction could not be further separated owing to the experimental difficulties involved. It was calculated, however, from the n_D values that it contained approximately 12 mg. of tetramethyl methyl-*d*-glucoside, corresponding to one non-reducing terminal group of about 250 ± 100 glucose residues.

Sweet Potato Starch.—The sweet potato starch was provided by The Laurel Starch Plant, Laurel, Miss., U.S.A., to whom our best thanks are due. The starch was a white powder very similar in general properties to potato starch. Iodometric titration showed the presence of some 18% of amylose.

The starch (50 g.) was methylated in an atmosphere of nitrogen (Hirst and Young, *loc. cit.*). After 5 methylations the crude dry product (40 g.), which had been purified by boiling with water and then with ether, was dissolved in chloroform and fractionated by the portionwise addition of light petroleum (b. p. 40—60°). Four fractions were obtained. Fraction (I), 4·2 g. (OMe, 43%); Fraction (II), 18·7 g. (OMe, 44·2%); Fraction (III), 12·1 g. (OMe, 44·3%); and Fraction (IV), 1·8 g. (OMe, 44·1%). These fractions were grey in colour and on standing became insoluble in solvents, swelling only in chloroform. For these reasons observations of optical activity were not possible. Fraction (II) (6·38 g.) was hydrolysed with methyl-alcoholic hydrogen chloride and the mixed glucosides (6·5 g.) were isolated after neutralisation with silver carbonate followed by filtration and removal of the solvent under reduced pressure. The syrup was dissolved in water (50 c.c.) and all the tetramethyl methyl-*d*-glucoside and some trimethyl methyl-*d*-glucoside were separated by continuous extraction for 6 hours with purified light petroleum (b. p. 40—60°). The syrupy mixture was dissolved in light petroleum (b. p. 60—80°) and chromatographed on active alumina, giving tetramethyl methyl-*d*-glucoside (259 mg., n_D^{16} 1·4440,

OMe, 61·2%). This corresponds to an average repeating unit of 28 ± 2 glucose residues (assuming a recovery of 93% of end-group).

We wish to thank the British Cotton Industry Research Association for the award of Shirley Fellowships to two of the authors (F. B. and T. G. H.).

THE UNIVERSITY, MANCHESTER, 13. [*Received, February 18th*, 1947.]

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6. *A Study of the Properties of Fluorine-substituted 5-Aminoacridines and Related Compounds. Part II. 5-Amino-2- and -4-trifluoromethyl acridines.*

By J. H. WILKINSON and I. L. FINAR.

5-Amino-2- and -4-trifluoromethylacridines have been prepared and their properties studied. The new derivatives did not exhibit any outstanding antibacterial activity.

THE study of the monofluoro-5-aminoacridines (Part I, *J.*, 1947, 759) has now been extended to include 5-*amino*-2- and -4-*trifluoromethylacridines*. Although the trifluoromethyl group has found useful applications in the preparation of dyes, numerous examples appearing in the patent literature, few trifluoromethyl compounds have been examined from the chemotherapeutic standpoint. Recently, however, Gilman and his collaborators (*J. Amer. Chem. Soc.*, 1946, **68**, 426) have reported the preparation of a number of such substances for examination for antimalarial activity, but we have been unable to find any report of antibacterial tests with compounds of this type. No trifluoromethyl derivatives of acridine have been described in the literature, though Bachman and Picha (*J. Amer. Chem. Soc.*, 1946, **68**, 2112) attempted the preparation of 2 : 5-dichloro-6- and -8-trifluoromethylacridines from 5-chloro-3′-trifluoromethyldiphenylamine-2-carboxylic acid, but were unable to separate the products in a pure state.

The compounds described in this paper were prepared from *m*-aminobenzotrifluoride which condensed with *o*-iodobenzoic acid, under the conditions described in Part I, to give 3′-*trifluoromethyldiphenylamine*-2-*carboxylic acid* in 61% yield. This underwent cyclisation with phosphoryl chloride to a mixture of 5-chloro-2- and -4-trifluoromethylacridines from which only the 2-*trifluoromethyl* isomer could be isolated in a pure state. However, when the mixed 5-chloroacridines were converted into the corresponding 5-amino-compounds by treatment with ammonium carbonate in phenol at 120° (Magidson and Grigorowski, *Ber.*, 1933, **66**, 866; Albert and Ritchie, *Org. Synth.*, 1942, **22**, 5), only 5-*amino*-2-*trifluoromethylacridine hydrochloride* was precipitated by the addition of acetone to the phenol melt. The 4-*trifluoromethyl* compound was obtained from the phenolic liquors by treatment with sodium hydroxide.

The relative proportions of the 2- and 4-substituted compounds resembled those obtained by cyclisation of 3′-methyldiphenylamine-2-carboxylic acid rather than those of the halogen-substituted derivatives :

Substituent	CF_3	Me	F	Cl
2-Derivative, %	35	20	60	60
4- ,, ...	65	80	40	40

The above figures were obtained as a result of experiments carried out in these laboratories. W were unable to confirm the ratio of 25 : 75 in favour of the 4-chloro-derivative reported by Lehmsted and Schräder (*Ber.*, 1937, **70**, 838).

The orientation of the trifluoromethyl derivatives has not been confirmed by unambiguous synthesis, but all the evidence we have leads to the conclusion that the more soluble compound is substituted in the 4 position. 4-Substituted 5-aminoacridines generally have lower melting points than their 2-isomers, thus : 2-chloro-, 277°; 4-chloro-, 270°; 2-fluoro-, 276°; 4-fluoro-, 266°; 2-nitro-, 290—295°; and 4-nitro-, 230°. In the case of the methyl derivatives, however, the difference is negligible : 2-methyl, 248°; 4-methyl, 248—249°. Albert and Ritchie (*J. Soc. Chem. Ind.*, 1941, **60**, 120) have shown that the hydrochlorides of 2- and 4-aminoacridine can be separated by virtue of the relatively high solubility of the latter, and we have demonstrated that this enhancement is general for a number of different substituents in the 4 position of 5-aminoacridine (see table).

The trifluoromethyl derivatives had m. ps. 246° and 229—230° whilst their hydrochlorides had solubilities of 0·2 and 3·3 g. per 100 c.c. respectively. There seems little doubt therefore that the former is substituted in the 2 position.

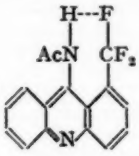
Solubility (g. per 100 c.c.) of Substituted 5-Aminoacridine Hydrochlorides in Water at 20°.

Substituent.	Position of substituent. 1.	2.	3.	4.
Fluorine [1]	0·55	0·2	0·1	2·8
Chlorine [2]	0·2	0·05	0·1	0·7
Nitro	—	0·2	—	0·4
Methyl	0·5 [3]	1·0	0·1 [2]	3·5 [2]

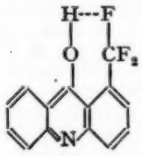
[1] Part I.
[2] Wilkinson and Finar, *J.*, 1946, 115.
[3] Albert and Gledhill, *Pharm. J.*, 1945, **154**, 127.

5-Amino-2-trifluoromethylacridine displayed no unexpected physical or chemical properties: it closely resembled the corresponding methyl derivative in solubility, salt formation, and reaction with acetic anhydride to give both *mono-* and *di-acetyl* derivatives. Like 5-aminoacridine it was hydrolysed to the corresponding *acridone* on prolonged refluxing with alcoholic potash (cf. Albert and Ritchie, *J.*, 1943, 458).

The 4-trifluoromethyl derivative proved to be highly soluble in most organic solvents but relatively sparingly so in acetone from which it crystallised readily. The *hydrochloride*, however, had an unexpectedly high solubility in this solvent. With acetic anhydride, the base readily gave the *monoacetyl* derivative under the conditions normally used for monoacetylation (Albert and Goldacre, *J.*, 1943, 454), but no diacetyl derivative could be isolated after refluxing the base or monoacetyl derivative with a large excess of acetic anhydride for several hours. The difficulty experienced in preparing the diacetyl derivative may be due to hydrogen bonding between the trifluoromethyl group and the neighbouring amino-group (I). It was considered



(I.)



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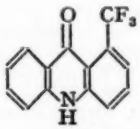

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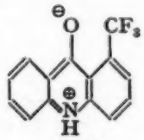

(IV.)

possible that a similar structure (II) might be found in 5-hydroxy-4-trifluoromethylacridine. However, the properties of this substance, prepared by alkaline hydrolysis of the corresponding 5-aminoacridine, so closely resembled those of acridone that it must be formulated as *4-trifluoromethylacridone*, *i.e.*, a resonance hybrid of (III) and (IV) (cf. Albert and Goldacre, *loc. cit.*; Hunter, *J.*, 1945, 809).

The monofluoro-5-aminoacridines and other substances described in Part I together with the compounds described in this paper have been examined for antibacterial activity against *Staph. aureus*, *B. coli*, and *Ps. pyocyanea*. The only compounds which compared favourably with 5-aminoacridine (cf. Rubbo, Albert, and Maxwell, *Brit. J. Exp. Path.*, 1942, **23**, 69) were 2-fluoro-5-amino-10-methylacridinium bromide which exhibited higher activity against *B. coli*, and 2-chloro-5-amino-10-methylacridinium bromide which gave higher activity against *Staph. aureus*. However, both compounds showed diminished activity against the latter organism in the presence of blood.

Experimental.

(M. ps. are corrected unless above 300°.)

3'-Trifluoromethyldiphenylamine-2-carboxylic Acid.—*o*-Iodobenzoic acid (49·6 g.) was dissolved in a solution of potassium carbonate (30 g.) in water (110 c.c.); *m*-aminobenzotrifluoride (35 g., 10% excess) and copper-bronze catalyst (3 g.) were added and the mixture was refluxed for 3 hours. Water (100 c.c.) was added and an equal volume distilled out to remove unreacted amine. The hot solution was filtered (charcoal) and the filtrate vigorously shaken with 30% ammonium chloride solution (200 c.c.) and cooled in ice. The precipitated ammonium salt was collected, washed with 30% ammonium chloride solution, and dissolved in 2N-sodium hydroxide (100 c.c.). The resulting solution was poured with stirring into N/2-hydrochloric acid (1 l.). The product separated as a gum which hardened on standing to a pale yellow powder (34·3 g., 61%). *3'-Trifluoromethyldiphenylamine-2-carboxylic acid* crystallised from 50% alcohol in pale yellow needles, m. p. 125° (Found: C, 59·8; H, 3·7; N, 4·95. $C_{14}H_{10}O_2NF_3$ requires C, 59·7; H, 3·56; N, 4·98%). The *p-nitrobenzyl* ester crystallised from 50% alcohol in pale yellow plates, m. p. 94° (Found: N, 6·55. $C_{21}H_{15}O_4N_2F_3$ requires N, 6·75%).

5-Chloro-2-trifluoromethylacridine.—3'-Trifluoromethyldiphenylamine-2-carboxylic acid (14 g.) was refluxed for 2 hours with phosphoryl chloride (25 c.c.) after which the excess of the latter was removed by distillation. The residue was dissolved in chloroform (60 c.c.) and the solution cooled with ice and

stirred with ammonia solution (100 c.c., *d* 0·880) for 30 minutes. The chloroform layer was separated, dried (K_2CO_3), and the solvent removed. The crude 5-chloroacridines (14 g.) were dissolved in a boiling mixture of alcohol (80 c.c.) and 2N-ammonia (10 c.c.), and the solid (6·95 g.) which separated was recrystallised from a similar mixture of ammonia and alcohol (40 c.c.). It was then dissolved in dry benzene (100 c.c.); the solution was passed through a column of alumina and the eluent evaporated. *5-Chloro-2-trifluoromethylacridine* crystallised from 90% alcohol in very pale yellow needles, m. p. 120° (Found: C, 59·6; H, 2·6; N, 5·1. $C_{14}H_7NClF_3$ requires C, 59·6; H, 2·5; N, 5·0%).

2-Trifluoromethylacridone.—5-Chloro-2-trifluoromethylacridine (2 g.) was heated on a steam-bath with N-hydrochloric acid (20 c.c.) for 2 hours. The precipitate was collected, washed with water, and dried at 100°. *2-Trifluoromethylacridone* crystallised from nitrobenzene in pale yellow elongated rectangular plates, m. p. > 360° (Found: C, 64·4; H, 3·1; N, 5·5. $C_{14}H_8ONF_3$ requires C, 63·9; H, 3·04; N, 5·3%). Yield, 1·56 g. (84%).

5-Amino-2-trifluoromethylacridine.—5-Chloro-2-trifluoromethylacridine (4 g.) was dissolved in phenol (6 g.) at 70°. Ammonium carbonate (1·5 g.) was added and the temperature raised to 120° for 1 hour. Acetone (50 c.c.) was added to the cooled solution to precipitate the hydrochloride of the product, which was dissolved in boiling water (400 c.c.) and the solution made alkaline with sodium hydroxide. *5-Amino-2-trifluoromethylacridine* crystallised from 70% alcohol in bright yellow prisms, readily soluble in acetone, m. p. 246° (Found: C, 64·4; H, 3·8; N, 10·6. $C_{14}H_9N_2F_3$ requires C, 64·1; H, 3·4; N, 10·7%). Yield, 2·86 g. (77%). The *hydrochloride monohydrate* crystallised in lemon-yellow prisms. m. p. 344—346° (decomp.), soluble in about 450 parts of water (Found: N, 8·8; Cl, 11·5; loss in weight at 130°/10 mm., 5·75. $C_{14}H_9N_2F_3,HCl,H_2O$ requires N, 8·85; Cl, 11·25; H_2O, 5·7%). The *monoacetyl* derivative crystallised in colourless needles from alcohol, m. p. 288° (Found: N, 9·4. $C_{16}H_{11}ON_2F_3$ requires N, 9·2%). The *diacetyl* derivative was obtained in colourless rhombs from alcohol, m. p. 151° (Found: C, 62·6; H, 4·3; N, 8·0. $C_{18}H_{13}O_2N_2F_3$ requires C, 62·5; H, 3·8; N, 8·1%). Both acetyl derivatives were readily soluble in alcohol giving solutions which exhibited a blue fluorescence in ultra-violet light. The addition of mineral acid produced a deep yellow colour (cf. Wilkinson and Finar, *J.*, 1946, 115).

5-Amino-4-trifluoromethylacridine.—The mixed 5-chloro-2- and -4-trifluoromethylacridines (2 g.) were dissolved in phenol (4 g.) at 70°. Ammonium carbonate (0·5 g.) was added and the temperature maintained at 120° for 1 hour. Acetone (30 c.c.) was added to the cooled mixture to precipitate the hydrochloride of 5-amino-2-trifluoromethylacridine which was dissolved in hot water and treated with sodium hydroxide to liberate the base (0·65 g., 35%). Acetone was removed from the liquors by distillation; the residue was treated with 2N-sodium hydroxide (50 c.c.) and set aside overnight. The solid was collected and ground with 2N-sodium hydroxide to remove the last traces of phenol. Yield, 1·14 g. (61%). It was purified by solution in benzene–alcohol (80 : 20) (100 c.c.) and passage through an alumina column. On concentration to about 10 c.c., *5-amino-4-trifluoromethylacridine* separated in small bright yellow prisms, m. p. 229—230°. Recrystallisation had no effect on the m. p. The product was readily soluble in alcohol and benzene but less soluble in acetone (Found: C, 64·3; H, 3·7; N, 10·8%). The *hydrochloride* was obtained in small lemon-yellow elongated rectangular prisms readily soluble in water and alcohol, m. p. 300—302° (decomp.) (Found: N, 9·7. $C_{14}H_9N_2F_3,HCl$ requires N, 9·7%). The *monoacetyl* derivative crystallised from benzene in colourless needles, m. p. 236° (Found: N, 9·4%). This derivative was also obtained when the base was refluxed for 3 hours with a large excess of acetic anhydride.

Hydrolysis with Alcoholic Potassium Hydroxide.—The 5-aminotrifluoromethylacridines (1 g.) were refluxed for 24 hours with 5N 80% alcoholic potassium hydroxide (100 c.c.). The cooled solutions were then acidified with 2N-acetic acid (300 c.c.) to precipitate the products. 2-Trifluoromethylacridone, identical with that obtained by hydrolysis of 5-chloro-2-trifluoromethylacridine, was obtained in 97% yield (Found: N, 5·45%). *4-Trifluoromethylacridone* (yield, 92%) crystallised from 80% aqueous pyridine in pale yellow rectangular prisms, m. p. above 360° (Found: N, 5·5%). Both trifluoromethylacridones were sparingly soluble in most organic solvents. Alcoholic solutions exhibited a blue fluorescence, which became vivid green on the addition of alkali.

Attempted Verification of Orientation.—2-Trifluoromethylacridone (0·5 g.) was refluxed with 70% sulphuric acid (10 c.c.) until the evolution of hydrogen fluoride ceased (cf. Rouche, *Bull. Acad. roy. Belg.*, 1927, **13**, 346). The cooled solution was poured into a mixture of crushed ice (50 g.) and alcohol (50 c.c.) and the solid collected (0·45 g.). Purification was effected by solution in N/2-sodium bicarbonate (10 c.c.) followed by precipitation with N/2-hydrochloric acid in the presence of alcohol (10 c.c.). Instead of the expected acridone-2-carboxylic acid, the product appeared to be partly sulphonated [Found: N, 4·3; S, 9·1. Calc. for $C_{14}H_9O_6NS$ (2-carboxyacridone-*x*-sulphonic acid): N, 4·4; S, 10·0%]. It was an orange-yellow powder, m. p. > 360°, sparingly soluble in organic solvents, but readily soluble in aqueous alkali giving a yellow solution which exhibited a vivid blue fluorescence on dilution. The same product was obtained when hydrolysis was effected with 50% sulphuric acid. We were unable to remove the sulphonic acid group by heating with hydrochloric acid in a sealed tube at 140°.

Attempted Preparation of Acridone-2-carboxylic Acid.—Bromoterephthalic acid (1·22 g., 0·005 g.-mol.) was dissolved in amyl alcohol (6 c.c.) and the solution treated with anhydrous potassium carbonate (1·05 g., 0·0075 g.-mol.). Aniline (0·6 g., 0·0065 g.-mol.) and copper-bronze catalyst (0·1 g.) were added and the mixture refluxed for 4 hours. Amyl alcohol and unreacted aniline were removed by steam distillation; the aqueous residue was clarified by filtration and the product (0·55 g.) precipitated by acidification with 2N-acetic acid. *Diphenylamine-2 : 5-dicarboxylic acid* crystallised from 90% alcohol in small bright yellow prisms, m. p. 318—319° (decomp.) (Found: N, 5·25. $C_{14}H_{11}O_4N$ requires N, 5·45%). An attempt to cyclise this substance to acridone-2-carboxylic acid by heating on a steam-bath with sulphuric acid gave an orange-coloured solid, containing sulphur, which resisted purification.

Determination of Dissociation Constants.—The pK_a values of both 5-aminoacridines were determined by the method described in Part I. The results were: 2-trifluoromethyl derivative, 8·3; 4-trifluoromethyl derivative, 7·9; a correction of 0·5 unit having been added to allow for the effect of the 50% alcohol used as solvent.

The authors wish to thank Mr. S. Bance, B.Sc., A.R.I.C. for the semi-micro-analyses, the Biological Division, May and Baker Ltd., for the biological results, and Dr. H. J. Barber and the Directors of May and Baker Ltd. for facilities kindly placed at the disposal of one of them (J. H. W.).

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7. *New Organic Sulphur Vesicants. Part I.* 2 : 2′-*Di*-(2-chloroethylthio)diethyl Ether.

By F. N. Woodward.

Davies and Oxford (*J.*, 1931, 224) showed that, at 100°, thiodiglycol and hydrogen chloride reacted to produce a mixture of (II; X = Cl) and an undistillable chloro-sulphide. The reaction has now been studied in detail and under a variety of conditions and the undistillable compound characterised as (III; X = Cl) which has been found to be highly vesicant to man. Bromo-, iodo-, cyano-, and thiocyanato-analogues of (III) have been prepared, and the interaction of hydrogen chloride and bromide with (III; X = Cl) and (III; X = OH) studied.

The conversion of thiodiglycol (I) into 2 : 2′-dichlorodiethyl sulphide (II; X = Cl) (mustard gas; H) by means of hot concentrated hydrochloric acid was first effected by Clarke (*J.*, 1912, **101**, 1585), thus overcoming the difficulties associated with the use of phosphorus trichloride in Meyer's original method (*Ber.*, 1886, **19**, 3259).

The process has since been the subject of many investigations as it was the sole method used by the Germans in the First World War for the manufacture of mustard gas. Davies and Oxford (*loc. cit.*) found that at 100° the reaction afforded a mixture of (II; X = Cl) and an undistillable oil, which they showed to be either (III; R = Cl), believed to be formed through the then

$S(CH_2{\cdot}CH_2{\cdot}OH)_2$ (I.) $S(CH_2{\cdot}CH_2X)_2$ (II.) $O(C_2H_4{\cdot}S{\cdot}C_2H_4X)_2$ (III.) $Cl{\cdot}C_2H_4{\cdot}O{\cdot}C_2H_4{\cdot}S{\cdot}C_2H_4{\cdot}S{\cdot}C_2H_4Cl$ (IV.)

unknown 2-chloroethyl 2′-hydroxyethyl sulphide, or, less probably, the isomeric 2-(2-chloroethoxy)-2′-(2-chloroethylthio)diethyl sulphide (IV), possibly produced by the scission of an intermediate sulphonium chloride.

The reaction was further studied in detail in these laboratories in 1932 when, although it was found impossible to repeat Davies and Oxford's findings in their entirety, it was proved that the main constituent of the undistillable oil was (III; X = Cl) and not (IV) and also that this compound had an empirical vesicant power of 325 compared with the arbitrary standard of 100 for (II; X = Cl) when tested in an inert solvent on the arms of 32 male volunteers.

Pure (III; X = Cl) has now been synthesised by the action of thionyl chloride in chloroform or dimethylaniline on (III; X = OH) obtained from dichlorodiethyl ether and the sodium salt of 2-hydroxyethanethiol. Its diphenoxy-derivative was found to be non-vesicant and identical with that obtained by Davies and Oxford, and further confirmation was obtained when Rosser (private communication) synthesised (IV) and found it to have properties unlike those of (III; X = Cl). The parent hydroxy-compound (III; X = OH) forms an oily *dimethiodide* and crystalline *bis-α-naphthyl-* and *-phenyl-urethanes*, whereas with concentrated hydrochloric acid at 100° a mixture of equal parts of (II; X = Cl) and (III; X = Cl) is obtained; similarly, excess 40% hydrobromic acid at 100° afforded a mixture of 75% of 2 : 2′-dibromodiethyl sulphide (II; X = Br) [*sulphilimine*, m. p. 161° (decomp.)] and 25% of crude 2 : 2′-di-(2-bromoethylthio)-diethyl ether.

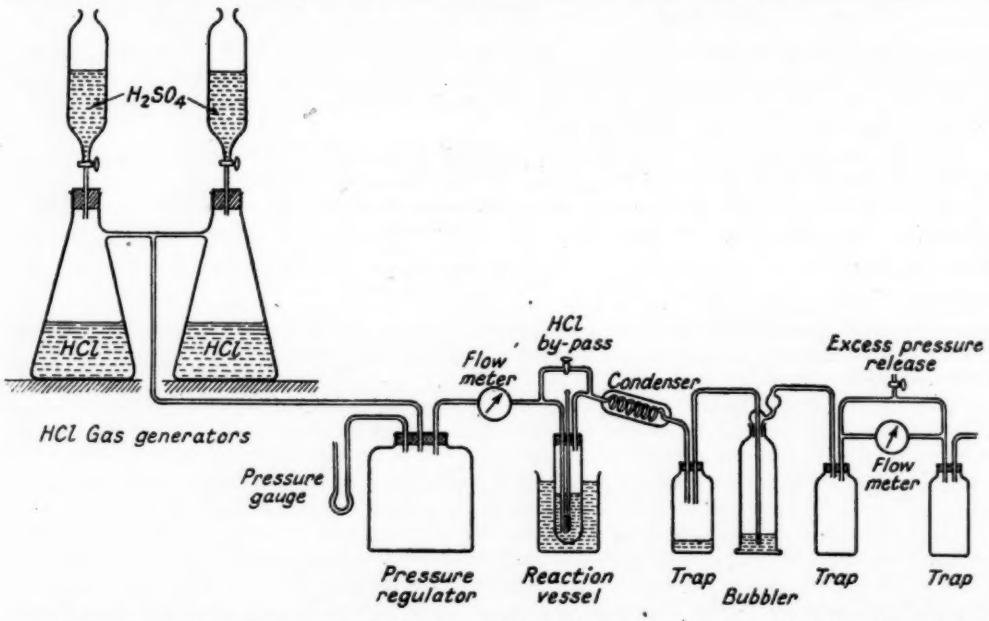
The *chloro-ether* (III; X = Cl) is a colourless liquid with a typical mustard odour, distilling with considerable decomposition at 174°/2 mm. but smoothly at 120°/0·001 mm. Its purification and physical properties will be described elsewhere. Unlike (III; X = OH) it does not react with alkyl iodides, chloramine-T, mercuric chloride or iodide, iodine, or bromine. It possesses the reactive chlorine atoms common to all β-chloroalkyl sulphides, and the *dicyano-*, *dithiocyanato-*, *di-s-tribromophenoxy-*, dipiperidino- (characterised as its *dipicrate*), and *di-iodo*-derivatives have been prepared by conventional methods; the first three on physiological examination were found to be non-vesicant. The chloro-compound (III; X = Cl) is practically unaffected by concentrated hydrochloric acid at 100°, although hydrogen chloride at elevated temperatures results in partial scission with formation of (II; X = Cl) and water. The controlled action of hydrogen bromide at 70° affords a mixture of (II; X = Br) and 2-chloro-2′-bromodiethyl sulphide, whilst excess results in complete conversion into (II;

X = Br). The interaction of hydrogen chloride or bromide and (III; X = OH) in its simplest form is therefore essentially a three-fold reaction, giving (II; X = Cl or Br) both directly and through the intermediate (III; X = Cl or Br).

A more complete study of the course of the reaction between hydrogen chloride and (I) and (III; X = OH) will be described elsewhere.

Experimental.

Action of Hydrogen Chloride on Thiodiglycol.—Davies and Oxford's method (*loc. cit.*) consisted in saturating thiodiglycol at 100—106° with hydrogen chloride; the lower, non-aqueous, layer was separated and distilled, yielding 56% of (II; X = Cl) and 44% of an undistillable chloro-sulphide. Repetitions of the preparation under conditions as nearly identical with their's as was possible from the short description given, afforded undistillable fractions differing materially in composition [Found (Oxford and Davies's results in parenthesis): Cl, 20·4, 20·6, 21·1, (23·7); S, 26·4, 26·9, 26·6, (25·7). Calc. for $C_8H_{16}OCl_2S_2$: Cl, 27·0; S, 24·3%] and yield [58, 60, 60 (44%)]. As the rate of passage of hydrogen chloride, quantity of thiodiglycol used, and time and temperature of reaction all affected the yield and quality of this product, the reaction was investigated under controlled conditions and with the standardised apparatus shown in the figure. The reaction was conducted in a 150-c.c. 1″ boiling-tube immersed in an oil-bath, hydrogen chloride was obtained from a sulphuric–hydrochloric acid generator,



and all gas flow-rates were measured by conventional U-type flow-meters. In the first series of experiments, pure distilled thiodiglycol (80 g.) was heated to the required temperature in the reaction vessel, and hydrogen chloride (99% HCl) passed through at such a rate (3 l./hr.) that a constant exhaust was maintained throughout the 75 minutes required to complete the reaction. A reflux condenser fitted above the reaction vessel allowed the aqueous reaction products to reflux at temperatures above 110°. In the second series the conditions were identical, except that the reflux condenser was replaced by a still-head to allow the volatile products to be removed by distillation continuously throughout the reaction. At the end of the reaction period, the product was cooled, drawn into cold water, washed, separated, dried by heating at 100°/50 mm. for 30 minutes, and weighed. The content of (II; X = Cl) was then determined by quantitative distillation, and the m. p. of the distilled (II; X = Cl) and that of the residue determined by the conventional Beckmann–Holleman cooling-curve method. The residue was analysed but not the distilled (II; X = Cl) as its m. p. in most cases closely approximated to 14·2°, that of the pure substance.

2 : 2′-*Di*-(2-*chloroethylthio*)*diethyl Ether* (III; X = Cl).—Redistilled 2 : 2′-dichlorodiethyl ether (47·7 g.) was slowly added down a reflux condenser to a solution of sodium (15 g.) in absolute alcohol (250 c.c.) to which had been added 2-hydroxyethanethiol (52 g.). After subsidence of the vigorous reaction, the mixture was heated on the steam-bath for 15 minutes and freed from precipitated salt by filtration; after removal of the alcohol by distillation, the residual salt in solution was precipitated by addition of acetone (200 c.c.). The solution was filtered and freed from solvent, crude 2 : 2′-*di*-(2-*hydroxyethylthio*)*diethyl ether* (III; X = OH) remaining as a yellow oil. It was purified by distillation at 215°/2·5 mm. Crystallisation from ether gave a white wax-like solid, m. p. 32°. Determination of sulphur by the Carius method was not practicable, and use was made of the method of Rosser and Woodward (*J.*, 1932, 2357) (Found: S, 28·5, 28·3; OH, 15·2, 15·2. $C_8H_{18}O_3S_2$ requires S, 28·3; OH, 15·0%).

Distilled and undistillable products of the interaction of thiodigycol and hydrogen chloride.

Reaction conditions.	Distilled (II; X = Cl): yield, %.	m. p.	Undistillable residue: yield, %.	m. p.	Found, %. Cl.	S.
60°; refluxed	94·2	12·2°	5·8	—	24·8	27·6
70° ,, ...	95·0	13·0	5·0	—	27·3	26·6
80° ,, ...	90·9	14·2	9·1(*a*)	− 7·2°	27·1	26·6
90° ,, ...	87·6	14·1	12·4	− 6·8	27·8	27·3
100° ,, ...	84·9	14·2	15·1	−11·7	26·9	26·2
110° ,, ...	—	—	—	−16·6	25·1	27·2
115°; distilled	57·0	10·7	43·0	−19	24·3	25·3
120° ,, ...	49·3	10·6	50·7	−20·1	23·6	24·3
120°; refluxed	57·8	13·5	42·2(*a*)	−20·7	24·5	26·3
130° ,, ...	15·0	—	85·0	—	28·2	17·4
130°; distilled	41·9	8·8	58·1	−19·9	23·1	27·0
140° ,, ...	23·0	5·2(*b*)	77·0	− 8·3(*b*)	18·0	26·6

(*a*) Diphenoxy-derivative, m. p. 60°, prepared. (*b*) Contained dithian.

An oily *dimethiodide* was obtained by prolonged heating at 100° with excess of methyl iodide (Found: I, 51·8. $C_{10}H_{24}O_2I_2S_2$ requires I, 50·0%). *Bis-α-naphthylurethane:* pinkish-white ill-defined crystals, m. p. 81·5°, from alcohol (Found*: C, 63·7; H, 5·7; S, 11·2. $C_{30}H_{32}O_4N_2S_2$ requires C, 63·8; H, 5·7; S, 11·3%). *Bisphenylurethane:* felted mass of small white needles from alcohol (Found*: C, 56·5; H, 6·2; S, 13·6. $C_{22}H_{28}O_4N_2S_2$ requires C, 56·9; H, 6·2; S, 13·8%).

Conversion of the hydroxy-sulphide into the chloro-compound (III; X = Cl) was more difficult than is usual with β-hydroxy-sulphides, on account of the ease with which decomposition takes place in presence of thionyl chloride alone or in ether–pyridine, alcoholic hydrogen chloride, or phosphorus pentachloride. The best method was to add slowly twice-distilled thionyl chloride, b. p. 75—76°/765 mm. (22 c.c.), to a vigorously stirred solution of the hydroxy-sulphide (28 g.) in chloroform (100 c.c.) which had been freshly distilled over phosphoric oxide, keeping the temperature below 40° throughout. When the evolution of sulphur dioxide had abated, the mixture was heated under reflux on a steam-bath for 20 minutes, and the solvent and excess of thionyl chloride were removed by distillation, followed by the passage of a rapid stream of dry air through the liquid at 90—100° for 30 minutes. The residual 2:2′-*di*-(2-*chloroethylthio*)*diethyl ether* (III; X = Cl) distilled with considerable decomposition at 174°/2 mm. but smoothly at 120°/0·001 mm. (Found: Cl, 26·6; S, 24·5. $C_8H_{16}OCl_2S_2$ requires Cl, 26·9; S, 24·3%). Diphenoxy-derivative: long lustrous needles, m. p. 60°, from alcohol; mixed m. p. with Davies and Oxford's sample (m. p. 55—57°) 58° (Found*: C, 63·4; H, 6·5; S, 17·0. Calc. for $C_{20}H_{26}O_3S_2$: C, 63·5; H, 6·9; S, 16·9%). *Di-s-tribromophenoxy*-derivative: blunt white needles, m. p. 70—71°, from alcohol–chloroform (2:1) (Found*: C, 28·3; H, 2·5; Br, 56·1. $C_{20}H_{20}O_3Br_6S_2$ requires S, 28·2; H, 2·3; Br, 56·4%). *Dipiperidino-dipicrate:* yellow blunt needles, m. p. 137—139°, from glacial acetic acid (Found*: C, 43·8; H, 5·1. $C_{30}H_{42}O_{16}N_8S_2$ requires C, 44·0; H, 5·1%). Attempted conversion of the hydroxy-ether (III; X = OH) into the chloro-ether (III; X = Cl) by heating with excess of concentrated hydrochloric acid resulted in an oil, 50% of which distilled at 96°/10 mm., the remainder being undistillable at 160°/2 mm. The former was shown to be (II; X = Cl), as it had m. p. 13·5°, analysed correctly (Found: Cl, 42·4. Calc. for $C_4H_8Cl_2S$: Cl, 42·8%), and formed a sulphilimine, m. p. 144° (Mann and Pope, *J.*, 1922, **121**, 1053, give m. p. 144·5°), which did not depress the m. p. of an authentic specimen. The undistillable residue was (III; X = Cl) (Found: Cl, 26·7%), affording a diphenoxy-derivative, m. p. 60°, undepressed by an authentic specimen. Similarly, from a heated mixture of 2:2′-di-(2-hydroxyethylthio)diethyl ether (1 vol.) and 40% aqueous hydrobromic acid (10 vol.) a light brown oil separated, 75% of which distilled at 115°/6 mm. The residue was impure 2:2′-*di*-(2-*bromoethylthio*)*diethyl ether* (III; X = Br) (Found: Br, 47·6. $C_8H_{16}OBr_2S_2$ requires Br, 45·3%), whilst the distillate, which set to a lustrous crystalline mass, m. p. 31°, was 2:2′-dibromodiethyl sulphide.

2:2′-*Dibromodiethyl Sulphide.*—In view of the discrepancy between the observed and recorded values for the b. p. (Steinkopf, Herold, and Stohr, *Ber.*, 1920, **53**, 1007, give b. p. 115°/1 mm.), this compound, b. p. 115°/6 mm., m. p. 31°, was synthesised by heating thiodiglycol with excess of aqueous hydrobromic acid in a manner identical with that used by Clarke (*loc. cit.*) in the synthesis of the chloro-analogue (II; X = Cl) (Found: Br, 64·3. Calc. for $C_4H_8Br_2S$: 64·4%). Both the suspected and the authentic specimen afforded a *sulphilimine*, fine needles, m. p. 161° (decomp.), from alcohol (Found*: C, 31·8; H, 3·7; S, 15·3. $C_{11}H_{15}O_2NBr_2S_2$ requires C, 31·6; H, 3·6; S, 15·3%).

Scission of 2:2′-*Di*-(2-*chloroethylthio*)*diethyl Ether.*—Hydrogen bromide was bubbled through the chloro-sulphide (60 g.) for 150 minutes at 100°. After removal of dissolved acid and the water formed, the residual oil all distilled at 140—141°/18 mm. and solidified to a crystalline mass, m. p. 31°, identified as 2:2′-dibromodiethyl sulphide through its sulphilimine, m. p. 160° (decomp.). By limiting the passage of hydrogen bromide to 30 minutes at 70°, a mixture was obtained from which 8 g. distilled at 125—130°/18 mm. The residue was unreacted (III; X = Cl), whilst the distillate was 2-chloro-2′-bromodiethyl sulphide (Kretov, *J. Russ. Phys. Chem. Soc.*, 1929, **61**, 2345, gave b. p. 125—132°/18 mm.) (Found: 0·2194 g. gave 0·3520 g. AgCl + AgBr; S, 15·4. Calc. for C_4H_8ClBrS: AgCl + AgBr, 0·3570 g.; S, 15·7%).

2:2′-*Di*-(2-*cyanoethylthio*)*diethyl Ether.*—The chloro-sulphide (10 g.) was added to a saturated solution of sodium cyanide in methyl alcohol (100 c.c.) and refluxed for 6 hours. After cooling, water (70 c.c.) was added and the oil deposited taken up in ether and dried (Na_2CO_3). Removal of the solvent left the *cyano*-compound as a pale yellow liquid, $d_4^{20°}$ 1·1283, which would neither distil nor crystallise (Found: S, 26·3. $C_{10}H_{16}ON_2S_2$ requires S, 26·2%).

2:2′-*Di*-(2-*thiocyanatoethylthio*)*diethyl Ether.*—By using a saturated methyl-alcoholic solution of

potassium thiocyanate in place of the sodium cyanide, the *thiocyanato-ether* was similarly obtained as a viscous liquid, $d_4^{20°}$ 1·2465, which could not be induced to crystallise (Found : S, 41·4. $C_{10}H_{16}ON_2S_4$ requires S, 41·5%).

2 : 2′-*Di*-(2-*iodoethylthio*)*diethyl Ether*.—By using an excess of an acetone solution of sodium iodide, the *iodo*-analogue was similarly obtained as an unstable oil, $d_4^{20°}$ 1·3372, decomposing on standing or attempted distillation (Found : I, 57·5. $C_8H_{16}OI_2S_2$ requires I, 57·0%).

Microanalyses marked * were carried out by Drs. Weiler and Strauss.

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H.M. Research Establishment, Sutton Oak. [*Received, January 9th*, 1947.]

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8. *New Organic Sulphur Vesicants. Part II. Analogues of* 2 : 2′-*Dichlorodiethyl Sulphide and* 2 : 2′-*Di*-(2-*chloroethylthio*)*diethyl Ether.*

By A. H. Williams and F. N. Woodward.

Homologues [(III), (VIII), (XII), (XVII), (XVIII), (XIX), (XX), (XXI), (XXII)] of the vesicants 2 : 2′-dichlorodiethyl sulphide and 2 : 2′-di-(2-chloroethylthio)diethyl ether having one or more methyl groups as substituents on the side chain have been synthesised, as have also compounds analogous to the latter in which its sulphur and chlorine atoms have been replaced by other atoms or groups. In the course of this work the difficulty experienced by Bennett and Whincop (*J.*, 1921, **119**, 1860) in converting (XI) into (XII) with thionyl chloride has been overcome, and the method of Boëseken, Tellegen, and Henriquez (*Rec. Trav. chim.*, 1931, **50**, 909) for the preparation of 2 : 3-dichloro-1 : 4-dioxan has been improved. (VI) and (VII), intermediates in the synthesis of (III), (XVII), and (XVIII), have been obtained in admixture by the interaction of propylene oxide and hydrogen sulphide. Most of the new chloro-sulphides synthesised have but slight vesicant power.

The only previously described bis-β-chloro-sulphides of the mustard gas (H) type having one or more methyl groups as substituents on the side chain are 2-chloroethyl 2-chloro-*n*-propyl (I), 2-chloroethyl 3-chloro-*n*-butane-2 (II), 2 : 2′-dichlorodi-*n*-propyl (III), and di-(3-chloro-*n*-butane-2) (IV) Coffey, *J.*, 1921, **119**, 94; Pope and Smith, *ibid.*, p. 396; Kranzlein and Covell, U.S.P. 1,570,262; Sylvester, unpublished). No corresponding analogues of the more powerful vesicant 2 : 2′-di-(2-chloroethylthio)diethyl ether have been recorded.

As part of a programme planned to determine the relationship between chemical constitution and vesicant power, a number of analogues of H and 2 : 2′-di-(2-chloroethylthio)diethyl ether have been synthesised and in some cases the physiological activity assessed.

Although Sylvester (*loc. cit.*) appears to have placed the orientation of (I), (II), and (IV) beyond dispute, no decisive evidence has yet been obtained as to the position of the methyl groups in (III). Pope and Smith (*loc. cit.*) assumed that the reaction between sulphur monochloride and propylene goes according to the left-hand side of the scheme

$$S_2Cl_2 + 2CHMe{:}CH_2 \longrightarrow \underset{\text{(III.)}}{S(CH_2{\cdot}CHMeCl)_2} \xleftarrow{HCl} \underset{\text{(VI.)}}{S(CH_2{\cdot}CHMe{\cdot}OH)_2} \xleftarrow{Na_2S} \underset{\text{(V.)}}{Cl{\cdot}CH_2{\cdot}CHMe{\cdot}OH}$$

On the other hand, Coffey (*loc. cit.*) making use of the interaction of propylene chlorohydrin (V) and sodium sulphide assumed, apparently without confirmatory evidence, that the chlorohydrin he used, obtained from allyl chloride and water (Oppenheim *Annalen Suppl.*, 1868, **6**, 367), was pure propylene-α-chlorohydrin (V). Pure (III) has now been obtained by Coffey's method from an authentic sample of (V) made from propylene oxide and hydrogen chloride (Smith, *Z. physikal. Chem.*, 1918, **93**, 59), and has been shown to be identical with that obtained by the earlier workers. The compound is best obtained, however, through 2 : 2′-*dihydroxydi*-n-*propyl sulphide* (VI) prepared, together with 2-*hydroxypropanethiol* (VII), by the interaction of propylene oxide and hydrogen sulphide.

2-*Chloroethyl* 2-*chloroisopropyl sulphide* (VIII) has been obtained as a colourless liquid, b. p. 88°/7 mm. (sulphilimine, m. p. 132°), by the following reactions :

$$Et{\cdot}CHO \xrightarrow[EtOH]{Br_2+} CHMeBr{\cdot}CH(OEt)_2 \xrightarrow{HS{\cdot}C_2H_4{\cdot}OH} HO{\cdot}C_2H_4{\cdot}S{\cdot}CHMe{\cdot}CH(OEt)_2$$

$$Cl{\cdot}C_2H_4{\cdot}S{\cdot}CHMe{\cdot}CH_2Cl \xleftarrow{SOCl_2} \underset{\text{(VIII.)}}{HO{\cdot}C_2H_4{\cdot}S{\cdot}CHMe{\cdot}CH_2{\cdot}OH} \xleftarrow{Al\ isopropoxide} HO{\cdot}C_2H_4{\cdot}S{\cdot}CHMe{\cdot}CHO \xleftarrow{HCl}$$

It closely resembles its β-analogue (IX) (b. p. 88°/4 mm.; *sulphilimine*, m. p. 129—130°).

2 : 2′-Di-(2-hydroxyethylthio)diethyl sulphide (XI) was obtained by Bennett and Whincop (*loc. cit.*) by condensing H with 2-hydroxyethanethiol (X) in alcoholic sodium ethoxide solution, but failed to convert it into the corresponding *chloro*-compound (XII). This conversion has now been effected by the controlled action of thionyl chloride in chloroform solution. (XII) readily forms a *platinochloride*, m. p. 136°, and its piperidino-derivative gave a *dipicrate*, m. p. 180°. In common with other β-chloro-sulphides it possesses extremely reactive chlorine atoms, completely removed by boiling alcoholic silver nitrate in 5 minutes and by boiling water in 45 minutes, and the *iodo-*, *thiocyanato-*, *phenoxy-*, α-naphthoxy-, β-*naphthoxy-*, s-*tribromophenoxy-*, and *thiophenoxy*-derivatives are easily obtained.

2 : 2′-*Di*-(2-*bromoethylthio*)*diethyl sulphide* was obtained by interaction of (XI) and phosphorus tribromide, but attempts to synthesise the corresponding cyano-compound by the interaction of H and 2-cyanoethanethiol failed, the reaction actually proceeding as follows :

$$S(C_2H_4Cl)_2 + 2NaS{\cdot}C_2H_4{\cdot}CN \longrightarrow S(CH_2{\cdot}CH_2)_2S + 2S(C_2H_4{\cdot}CN)_2 + 2NaCl$$

Oxidation of (XII) afforded the *trisulphone*, $SO_2(C_2H_4{\cdot}SO_2{\cdot}C_2H_4Cl)_2$. 2 : 2′-*Di*-(2-*chloroethylthio*)*diethyl sulphoxide*, *sulphone*, *disulphide* (XIV), and the 1 : 4-*dioxan* have been obtained by methods similar to those employed in the synthesis of (XII). The requisite initial chloro-compounds were obtained by recognised methods with the exception of 2 : 3-dichloro-1 : 4-dioxan required for the synthesis of the last. Although this had been obtained by Boëseken, Tellegen, and Henriquez (*loc. cit.*), repetition of their work showed that higher chloro-derivatives were always obtained in quantity, a fact subsequently borne out by the work of Butler and Cretcher (*J. Amer. Chem. Soc.*, 1932, **54**, 2987), Summerbell and Christ (*ibid.*, p. 3778), and Baker (*J.*, 1932, 2666). By using mixed sulphuryl chloride and sulphur monochloride in the presence of aluminium chloride as described by Silberrad (*J.*, 1922, **121**, 1016), the chlorination was easily controlled and afforded the desired dichlorodioxan in good yield in 3 hours. The 2 : 2′-dichlorodiethyl disulphide (XV) required for the synthesis of (XIV) was obtained by Bennett's method (*J.*, 1921, **119**, 424) although we separated and distilled the intermediate *hydroxy*-compound (XVI), which readily afforded a *bis*-α-*naphthylurethane* and *diphenoxy-*, *dieugenoxy-*, and *di*-s-*tribromophenoxy*-derivatives.

(I), (XVII), and (XVIII) have been prepared by the interaction of (VII) and the appropriate chloro-compound, followed by the controlled action of thionyl chloride on the hydroxy-sulphide formed. Similarly, (III) with (X) and with (VII) affords (XX) and (XXI), respectively, whilst subjection of (VI) to the action of hydrogen chloride at 100° affords a mixture of (III) and (XIX).

The physiological activity of certain of these analogues was assessed by the Physiological Section, Chemical Defence Experimental Station, Porton. The " empirical vesicant power " compared with an arbitrarily chosen standard H = 100, was obtained by comparison of the size of vesicles resulting from the application of the test and standard compounds in an inert solvent to the fore-arms of male volunteers. Table I gives details of the compounds tested.

TABLE I.

	M. p.	B. p.	Empirical vesicant power (H = 100).
2 : 2′-Dichloro-di-*n*-propyl sulphide (III)	−40°	105°/10 mm.	10
2-Chloroethyl 2-chloro-*n*-propyl sulphide (VIII)	−23	88/4 mm.	30
2-Chloroethyl 2-chloro*iso*propyl sulphide (I)	−24·5	88/7 mm.	50
2 : 2′-Di-(2-chloro-*n*-propylthio)diethyl ether (XVII)	—	95—98/0·02 mm.	20
2 : 2′-Di-(2-chloro-*n*-propylthio)di*iso*propyl ether (XIX)	—	90/0·01 mm.	10
2 : 2′-Di-(2-chloroethylthio)diethyl sulphide (XII)	73—75	—	20
2 : 2′-Di-(2-chloro-*n*-propylthio)diethyl sulphide (XVIII)	43·5	—	30
2 : 2′-Di-(2-chloro-*n*-propylthio)di-*n*-propyl sulphide (XXI)	—	108—109/0·02 mm.	20
2 : 2′-Di-(2-chloroethylthio)di-*n*-propyl sulphide (XX)	—	—	50

EXPERIMENTAL.

2-Hydroxypropanethiol (VII) *and* 2 : 2′-*Dihydroxydi*-n-*propyl Sulphide* (VI).—The apparatus and technique described by Woodward for the production of thiodiglycol (in the press) being used, liquid propylene oxide was introduced at 0·7 c.c. per min. and hydrogen sulphide throughout at 45 l./hr., the reaction being continuous at 60°. In the course of six experiments, 680 g. of propylene oxide were used, giving a product (948 g.) which on distillation gave *2-hydroxypropanethiol* (488 g.), b. p. 44·5—45°/8 mm.; $n_D^{18\cdot0°}$ 1·4850 (Found : S, 35·1; SH, 35·6. C_3H_8OS requires S, 34·8; SH, 35·9%), and 2 : 2′-*dihydroxydi*-n-*propyl sulphide* (390 g.), b. p. 125°/4 mm. (Found : S, 21·3; OH, 22·4. $C_6H_{14}O_2S$ requires S, 21·3; OH, 22·7%).

2 : 2′-*Dichlorodi*-n-*propyl Sulphide* (III).—By proceeding essentially according to Smith (*loc. cit.*),

2-chloro*iso*propyl alcohol was obtained, and the fraction, b. p. 126—128°, shown to be substantially pure by oxidation with nitric acid to chloro*iso*nitrosoacetone (Henry, *Bull. Acad. roy. Belg.*, 1903, **6**, 397; 1902, **5**, 535). The chlorohydrin (20 g.) was condensed with sodium sulphide (8·3 g.) in alcohol (70 c.c.), the mixture being boiled under reflux for 10 minutes. The precipitated salt was filtered off, and after removal of the solvent the 2 : 2′-dihydroxydi-*n*-propyl sulphide was distilled under reduced pressure, b. p. 114°/3 mm.

The hydroxy-sulphide (50 g.) obtained by either of the above methods was dissolved in chloroform (200 c.c.) and treated dropwise with thionyl chloride (62 c.c., 20% excess). After subsidence of the vigorous reaction, the mixture was boiled over the water-bath for 30 minutes, and the solvent then removed by distillation. The 2 : 2′-*dichlorodi*-n-*propyl sulphide* was once distilled under reduced pressure (Found : Cl, 37·6. $C_6H_{12}SCl_2$ requires Cl, 37·9%). Its sulphilimine, crystallised from alcohol, had m. p. 166° and was identical with that obtained from the chloro-sulphide prepared by the method of Pope and Smith (*loc. cit.*).

2-*Chloroethyl* 2-*Chloro*iso*propyl Sulphide* (VIII).—Bromine (45 c.c.), dissolved in ethyl acetate (100 c.c.), was added dropwise during 3 hours to a stirred mixture of propaldehyde (58 g.) and ethyl acetate (300 c.c.) kept between — 5° and 0° by immersion in ice–salt. When addition was complete, the mixture was poured into absolute alcohol (500 c.c.) and kept at room temperature for 18 hours. Some solvent (500 c.c.) was then removed under vacuum on a water-bath at 70°. The remaining solution was added to potassium carbonate (300 g.) dissolved in water (300 c.c.), and the precipitated oil separated quickly and washed with water. After drying (Na_2SO_4), the liquid was distilled in a vacuum, and the fraction, b. p. 60—68°/11 mm., separated. This on redistillation gave α-bromopropaldehyde diethyl acetal, b. p. 67°/13 mm. To sodium (8·2 g.) dissolved in absolute alcohol (200 c.c.) was added 2-hydroxyethanethiol (27·8 g.), followed by the acetal (75 g.). No immediate precipitation of sodium bromide occurred, and the mixture was refluxed on the water-bath for 25 hours before the odour of the bromoacetal disappeared completely. The precipitated sodium bromide was filtered off, and the alcohol removed under reduced pressure. The residual dark oil, distilled in a vacuum, gave a light yellow distillate, b. p. 86—90°/0·5 mm. On redistillation, α-(2-*hydroxyethylthio*)*propaldehyde diethyl acetal* was obtained as a colourless liquid, b. p. 87°/0·5 mm. (Found : S, 15·6. $C_9H_{20}O_3S$ requires S, 15·4%). The acetal sulphide (40 g.) was dissolved in 3% hydrochloric acid (1200 c.c.) and allowed to stand for 24 hours. After neutralisation with magnesium carbonate, saturation with salt, and filtration, the aqueous solution (1400 c.c.) was extracted with five 300 c.c. portions of ether. The ethereal extract, after drying (Na_2SO_4), was freed from solvent on the water-bath, the last traces being removed in a vacuum. α-(2-*Hydroxyethylthio*)-*propaldehyde* remained as a colourless oil (Found : S, 23·6. $C_5H_{10}O_2S$ requires S, 23·9%). Reduction of the aldehyde was carried out with aluminium *iso*propoxide by the method of Young, Hartung, and Crossley (*J. Amer. Chem. Soc.*, 1936, **58**, 100). On distillation of the reaction product, the fraction of b. p. 135—143°/5 mm. was collected and redistilled to give relatively pure 2-*hydroxyethyl* 2-*hydroxy*iso-*propyl sulphide*, b. p. 136—137°/5 mm. (Found : S, 22·2; OH, 22·8. $C_5H_{12}O_2S$ requires S, 23·5; OH, 25·0%). Conversion into the chloro-compound, b. p. 105°/12 mm., followed in the usual manner. The sulphilimine, from aqueous alcohol, had m. p. 132°; admixture with *p*-toluenesulphonamide depressed this to m. p. 115°, whilst addition of the sulphilimine of the isomeric 2-chloroethyl 2-chloro-*n*-propyl sulphide (m. p. 130°) gave mixed m. p. 128°.

2 : 2′-*Di*-(2-*chloroethylthio*)*diethyl Sulphide* (XII).—2 : 2′-Di-(2-hydroxyethylthio)diethyl sulphide (9·5 g.; 1 mol.), prepared by the method of Bennett (*loc. cit.*), in chloroform (100 c.c.) was treated dropwise with redistilled thionyl chloride (11·5 g.; 20% excess), a vigorous reaction occurring. After 30 mins.' heating over the steam-bath, the solvent and excess of thionyl chloride were removed by distillation, and the residual solid, after two crystallisations from alcohol–chloroform (1 : 2) and finally from absolute methyl alcohol, was obtained as silvery scales, m. p. 73—75° (Found : S, 34·0; Cl, 25·5. $C_8H_{16}Cl_2S_2$ requires S, 34·4; Cl, 25·4%). Its *platinochloride*, m. p. 136°, separated as a mustard-coloured, amorphous solid 10 minutes after a solution of platinic chloride (0·5 g.) in acetone was added to the chloro-compound (0·1 g.) also in acetone (Found : Pt, 31·7. $C_8H_{16}Cl_6S_2Pt$ requires Pt, 31·7%). The piperidide, roseate crystals from alcohol, was converted into its *picrate*, m. p. 180° (decomp.), micro-crystals from alcohol (Found : C, 43·5; H, 5·2. $C_{30}H_{32}O_{14}N_8S_2$ requires C, 43·7; H, 5·0%).

Several *ethers* (see Table II) were obtained by the following general method : 2 : 2′-di-(2-chloroethylthio)diethyl sulphide (0·01 mol.) in alcohol (20 c.c.) was refluxed for 1 hour with the phenol (0·02 mol.) in the requisite amount of alcoholic sodium ethoxide, and the ether separated by addition of water (60 c.c.).

TABLE II.

Ethers and thio-ethers from $S(C_2H_4{\cdot}S{\cdot}C_2H_4Cl)_2$.

Ether.	Crystal form from EtOH–$CHCl_3$.	M. p.	Formula.	Found, %. C.	H.	S.	Required, %. C.	H.	S.
Phenoxy-	Colourless rhombs	59°	$C_{20}H_{26}O_2S_2$	60·3	6·2	—	60·9	6·6	—
α-Naphthoxy-	Lustrous needles	56	—	—	—	—	—	—	—
β-Naphthoxy-	Silvery plates	122	$C_{28}H_{30}O_2S_2$	—	—	19·1	—	—	19·4
s-*Tribromo-phenoxy-*	Irregular plates	107	$C_{20}H_{20}O_2Br_6S_2$	—	—	11·5§	—	—	11·1
Eugenoxy-	Felted needles	86	$C_{28}H_{38}O_4S_2$	62·5	7·1	—	62·9	7·1	—
Thiophenoxy-	Silvery leaflets	92—94	$C_{20}H_{26}S_5$	—	—	37·3	—	—	37·5

§ Found : Br, 55·3. $C_{20}H_{20}O_2Br_6S_2$ requires Br, 55·3%.

2 : 2′-*Di*-(2-*iodoethylthio*)*diethyl Sulphide*.—The chloro-compound (1·3 g.) in methyl alcohol (10 c.c.) was refluxed with a saturated solution of sodium iodide in methyl alcohol (60 c.c.) for 10 minutes. The precipitated salt, after filtration, was extracted with boiling chloroform (50 c.c.), and the residual *iodo*-compound obtained on removal of solvent from the combined solution and washings separated as a white solid, m. p. 102—103°, which, unlike its hydroxy-analogue and 2 : 2′-di-iododiethyl sulphide, is perfectly stable (Found : I, 53·6. $C_8H_{16}I_2S_2$ requires I, 55·0%).

2 : 2′-*Di*-(2-*thiocyanatoethylthio*)*diethyl Sulphide*.—The chloro-compound (1·8 g.) in acetone (20 c.c.) was refluxed for 16 hours with a saturated acetone solution of potassium thiocyanate (60 c.c.), the solvent then removed by distillation, and water (60 c.c.) added. The oil which separated was taken up in ether, the solution dried (Na_2SO_4), and the crude *thiocyanato*-compound obtained by removal of the solvent was crystallised from alcohol–chloroform (4 : 1), from which it separated as glistening plates, m. p. 52° (Found * : C, 37·2; H, 5·2; S, 49·7. $C_{10}H_{16}N_2S_4$ requires C, 37·0; H, 4·9; S, 49·4%).

Attempted Synthesis of 2 : 2′-*Di*-(2-*cyanoethylthio*)*diethyl Sulphide*.—Interaction of ethylene cyanohydrin (0·2 mol.) and 2 : 2′-dichlorodiethyl sulphide (0·1 mol.) in presence of the theoretical amount of alcoholic sodium ethoxide afforded an oil on removal of the solvent from the filtered reaction mixture. This on crystallisation from alcohol yielded long needles of dithian, m. p. 110° (mixed with authentic specimen, m. p. 110°), and gradual addition of chloroform to the mother-liquors thus obtained precipitated crude 2 : 2′-dicyanodiethyl sulphide which, on recrystallisation from alcohol–chloroform (1 : 1), was obtained as plates, m. p. 28° (mixed m. p. with authentic sample kindly supplied by Dr. R. J. Rosser, 28°).

2 : 2′-*Di*-(2-*chloroethylsulphonyl*)*diethyl Sulphone*.—To a solution of 2 : 2′-di-(2-chloroethylthio)diethyl sulphide (1·0 g.) in glacial acetic acid (50 c.c.) was added 30% hydrogen peroxide (24 c.c.; 6 mols.) during 1 hour with intermittent shaking. After removal of the solvent by distillation, the crude *tri-sulphone*

Compound.	Solvent.	Crystalline form.	M. p. or b. p.	Formula.	Found, %		Required, %.
2 : 2′-Di-(2-hydroxyethylthio)diethyl sulphoxide	—	Long needles	57°	$C_8H_{18}O_3S_3$	S	37·3	37·2
2 : 2′-Di-(2-chloroethylthio)diethyl sulphoxide	Acetone–alcohol	Microcrystals	63	$C_8H_{16}OCl_2S_3$	Cl	24·2	24·0
2 : 2′-Di-(2-hydroxyethylthio)diethyl sulphone	Acetone	Plates	85—86	$C_8H_{18}O_4S_3$	S	35·8	35·0
2 : 2′-Di-(2-chloroethylthio)diethyl sulphone	Alcohol	Prisms	107—109	$C_8H_{16}O_2Cl_2S_3$	S	31·1	30·9
2 : 2′-Di-(2-hydroxyethylthio)diethyl disulphide	Alcohol	Amorphous powder	79—81	$C_4H_9OS_2$	S	48·7§	46·7
2 : 2′-Di-(2-hydroxy-*n*-propylthio)diethyl sulphide	Benzene–light petroleum	—	59	$C_{10}H_{22}O_2S_3$	S	35·7	35·6
2 : 2′-Di-(2-chloro-*n*-propylthio)diethyl sulphide (XVIII)	Light petroleum	—	43·5	$C_{10}H_{20}Cl_2S_3$	Cl	23·1	23·1
2 : 3-Di-(2-hydroxyethylthio)-1 : 4-dioxan †	—	Oil	—	$C_8H_{16}O_4S_2$	S	25·8	26·7
2 : 3-Di-(2-chloroethylthio)-1 : 4-dioxan	—	—	138—141/15 mm.	$C_8H_{14}O_2Cl_2S_2$	S Cl	23·1 25·5	23·1 25·6
2-Hydroxyethyl 2-hydroxypropyl sulphide	—	—	154/8 mm.	$C_5H_{12}O_2S$	S OH	23·5 25·2	23·5 25·0
2-Chloroethyl 2-chloro-*n*-propyl sulphide (I)	—	—	88/4 mm.	$C_5H_{10}Cl_2S$	Cl	41·2	41·1
2 : 2′-Di-(2-hydroxy-*n*-propylthio)diethyl ether	—	—	217—218/5 mm.	$C_{12}H_{26}O_3S_2$	S	25·5	25·2
2 : 2′-Di-(2-chloro-*n*-propylthio)diethyl ether (XVII)	—	—	95—98/0·02 mm.	$C_{10}H_{20}Cl_2OS_2$	Cl	24·1	24·4
2 : 2′-Di-(2-hydroxyethylthio)di-*n*-propyl sulphide	—	—	240/1·5 mm.	$C_{10}H_{22}O_2S_3$	S	35·8	35·6
2 : 2′-Di-(2-chloroethylthio)di-*n*-propyl sulphide (XX)	—	—	—	$C_{10}H_{18}Cl_2S_3$	Cl	23·0	23·2
2 : 2′-Di-(2-hydroxy-*n*-propylthio)di-*n*-propyl sulphide	—	—	210/0·5 mm.	$C_{12}H_{26}O_2S_3$	S	32·3	32·2
2 : 2′-Di-(2-chloro-*n*-propylthio)di-*n*-propyl sulphide (XXI)	—	—	108—109/0·02 mm. (slight decomp.)	$C_{12}H_{24}Cl_2S_2$	Cl	22·1	21·2

§ High S content due to dissolved dithian (cf. Bennett, *J.*, 1921, **119**, 424).

† *Bis-α-naphthylurethane*, m. p. 152° from benzene (Found : S, 11·2. $C_{30}H_{30}O_4N_2S_2$ requires S, 11·1%).

remained as a white solid, sparingly soluble in water, rectified spirits, and glacial acetic acid. After two crystallisations from the last, it was obtained in white nodules, m. p. 174·5° (Found: S, 25·2; Cl, 19·5. $C_8H_{16}O_6Cl_2S_2$ requires S, 25·5; Cl, 19·2%).

2 : 2′-*Di*-(2-*bromoethylthio*)*diethyl Sulphide*.—2 : 2′-Di-(2-hydroxyethylthio)diethyl sulphide (4 g.) in chloroform (60 c.c.) was refluxed for 2 hours with phosphorus tribromide (8 g.), the solvent removed, water (50 c.c.) added, and the residue extracted with chloroform. The extract, after drying (Na_2SO_4) and removal of solvent, left a solid which, after crystallising twice from chloroform, had m. p. 87·5—88·5° (Found: Br, 43·0. $C_8H_{16}Br_2S_2$ requires Br, 43·4%).

The *compounds* (Table, p. 41) were prepared by the general method used in the synthesis of 2 : 2′-di-(2-chloroethylthio)diethyl sulphide and its hydroxy-precursor.

Of the requisite starting materials, 2 : 2′-dichlorodiethyl sulphoxide and sulphone were obtained by the methods of Helfrich and Reid (*J. Amer. Chem. Soc.*, 1920, **42**, 1211) and Steinkopf, Herold, and Stohr (*Ber.*, 1920, **53**, 1007), respectively.

2 : 2′-Dichlorodiethyl disulphide was prepared by Bennett's method (*loc. cit.*), except that the intermediate 2 : 2′-*dihydroxydiethyl disulphide* was distilled at 158—163°/3·5 mm. (Found: S, 40·9. $C_4H_{10}O_2S_2$ requires S, 41·5%). The *bis-α-naphthylurethane* had m. p. 150—152° (Found *: C, 63·7; H, 5·1; N, 5·6; S, 13·0. $C_{26}H_{24}O_4N_2S_2$ requires C, 63·4; H, 4·9; N, 5·7; S, 13·0%). Conversion of the hydroxy-disulphide into the chloro-compound, b. p. 132—134°/5 mm., is best effected by means of thionyl chloride. The *di-s-tribromophenoxy*-derivative crystallised from methyl alcohol, m. p. 76° (Found: Br, 61·3. $C_8H_6OBr_3S$ requires Br, 61·6%). The *dieugenoxy*-derivative was obtained as long rhombs, m. p. 97°, from methyl alcohol–chloroform (1 : 2) (Found: S, 14·7. $C_{12}H_{18}O_3S$ requires S, 14·4%).

2 : 3-*Dichloro*-1 : 4-*dioxan*.—The method of Boëseken, Tellegen, and Henriquez (*loc. cit.*), involving passage of chlorine through dioxan (200 g.) for 16 hours at 90°, was only partly successful, as higher chloro-compounds were principally obtained. The reaction proceeded smoothly, however, and was completed in 50 minutes, when sulphur monochloride (1·5 g.) in sulphuryl chloride (150 g.) was slowly added down a reflux condenser to a mixture of dioxan (88 g.) and aluminium chloride (10 g.) at 70°. After cooling, the mixture was treated with water and extracted with benzene, the extract dried ($CaCl_2$), and solvent removed; fractional distillation afforded unreacted dioxan (28 g.) and 2 : 3-dichloro-1 : 4-dioxan (25 g.), b. p. 82·5—84°/14 mm. (Boëseken *et al.* give b. p. 82·4°/14 mm.).

2 : 2′-*Di*-(2-*chloro*-n-*propylthio*)*diisopropyl Ether* (XIX).—Distillation of the reaction product obtained by the action of hydrogen chloride on 2 : 2′-dihydroxydi-*n*-propyl sulphide at 100° during 1 hour afforded 2 : 2′-dichlorodi-*n*-propyl sulphide, b. p. 100°/7 mm., and the desired *ether*, b. p. 90°/0·01 mm. (Found: Cl, 22·4. $C_{12}H_{24}Cl_2OS_2$ requires Cl, 22·4%).

Microanalyses marked * were carried out by Drs. Weiler and Strauss.

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9. *New Organic Sulphur Vesicants. Part III. Homologues of 2 : 2′-Di-(2-chloroethylthio)diethyl Ether.*

By R. Brown and F. N. Woodward.

The powerful vesicants 2 : 2′-dichlorodiethyl sulphide and 2 : 2′-di-(2-chloroethylthio)-diethyl ether are the first two members of the series having the general formula (I). The third, fourth, fifth, and sixth members have now been prepared.

The four compounds mentioned above (I; $n = 2$, 3, 4, and 5) have not hitherto been described.

$$Cl\cdot[C_2H_4\cdot S\cdot C_2H_4\cdot O]_n\cdot C_2H_4\cdot S\cdot C_2H_4Cl \quad (I.)$$

1 : 17-*Dichloro*-6 : 12-*dioxa*-3 : 9 : 15-*trithiaheptadecane* * (I; $n = 2$) and 1 : 23-*dichloro*-6 : 12 : 18-*trioxa*-3 : 9 : 15 : 21-*tetrathiatricosane* (I, $n = 3$) have now been synthesised through the following stages, starting from 2 : 2′-*di*-(2-*hydroxyethoxy*)*diethyl sulphide* (II) and 2-*hydroxy*-2′-*mercaptodiethyl ether* (V) obtained by the interaction of diethylene chlorohydrin and sodium hydrogen sulphide in alcoholic solution.

$$S(C_2H_4\cdot O\cdot C_2H_4\cdot OH)_2 \xrightarrow{SOCl_2} S(C_2H_4\cdot O\cdot C_2H_4Cl)_2 \xrightarrow{NaS\cdot C_2H_4\cdot OH} S(C_2H_4\cdot O\cdot C_2H_4\cdot S\cdot C_2H_4\cdot OH)_2 \xrightarrow{SOCl_2} (I;\ n = 2)$$

(II.) (III.) (IV.)

$$HS\cdot C_2H_4\cdot O\cdot C_2H_4\cdot OH \xrightarrow[NaOEt]{O(C_2H_4Cl)_2} O(C_2H_4\cdot S\cdot C_2H_4\cdot O\cdot C_2H_4\cdot OH)_2 \xrightarrow{SOCl_2} O(C_2H_4\cdot S\cdot C_2H_4\cdot O\cdot C_2H_4Cl)_2$$

(V.) (VI.) (VII.)

$$\downarrow NaS\cdot C_2H_4\cdot OH$$

$$(I;\ n = 3) \xleftarrow{SOCl_2} O(C_2H_4\cdot S\cdot C_2H_4\cdot O\cdot C_2H_4\cdot S\cdot C_2H_4\cdot OH)_2$$

(VIII.)

* This terminology, sanctioned by the International Union of Chemistry (see *J.*, 1931, 1607), is adopted for the longer hetero-chains.—Editor.

Attempts to synthesise the fifth and sixth members of the series by a similar series of reactions starting from (III) and (VII) were unsuccessful on account of the difficulties encountered in purifying the essential intermediate compounds $S(C_2H_4{\cdot}O{\cdot}C_2H_4{\cdot}S{\cdot}C_2H_4{\cdot}O{\cdot}C_2H_4Cl)_2$ and $O(C_2H_4{\cdot}S{\cdot}C_2H_4{\cdot}O{\cdot}C_2H_4{\cdot}S{\cdot}C_2H_4{\cdot}O{\cdot}C_2H_4{\cdot}S{\cdot}C_2H_4Cl)_2$ neither of which could be distilled or crystallised. An alternative route was therefore chosen dependent upon *2-mercapto-2′-(2-hydroxyethylthio)diethyl ether* (IX) as starting material. This was obtained in 40% yield, together with 2 : 2′-di-(2-hydroxyethylthio)diethyl ether, by treating di-2-mercaptoethyl ether with one equivalent each of sodium ethoxide and ethylene chlorohydrin. The parent hydroxy-compounds of the desired 1 : 29-*dichloro*-6 : 12 : 18 : 24-*tetraoxa*-3 : 9 : 15 : 21 : 27-*pentathianonacosane* (I; $n = 4$) and 1 : 35-*dichloro*-6 : 12 : 18 : 24 : 30-*pentaoxa*-3 : 9 : 15 : 21 : 27 : 33-*hexathiapentatriacontane* (I; $n = 5$) were obtained by interaction of the sodium salt of (IX) with (III) and (VII), respectively. Conversion into the chloro-compounds and the formation of various derivatives followed the usual lines. Confirmation of the structure of various intermediates was obtained by means of the alternative synthesis of (VIII) from di-2-chloroethyl ether and (IX). Another structural confirmation was obtained by the preparation of the methylthio-ether of (I; $n = 2$) by the two routes :

$$(\text{I};\ n = 2) + 2\text{SMeNa} \longrightarrow S(C_2H_4{\cdot}O{\cdot}C_2H_4{\cdot}S{\cdot}C_2H_4SMe)_2 \longleftarrow (\text{III}) + 2\text{NaS}{\cdot}C_2H_4{\cdot}SMe$$

The chloro-compounds (I; $n = 2$, 3, 4, and 5) are colourless, low-melting solids which, like their derivatives, are difficult to purify; their crystallising power is low, and preparations melting 5—10° below their true m. p.s were frequently encountered and the m. p.s could not be raised by repeated crystallisation. This fact explains the necessity for rigid purification of intermediates in the above syntheses.

Experimental.

Diethylene Chlorohydrin.—A modification of the method of Fourneau and Ribas (*Bull. Soc. chim.*, 1927, **41**, 1046) afforded the chlorohydrin in 35% yield. Ethylene oxide was distilled into a mixture of ethylene chlorohydrin (500 c.c.) and concentrated sulphuric acid (9 c.c.) in a flask fitted with an inlet tube and a reflux condenser cooled with solid carbon dioxide–alcohol, during ½ hour. The contents of the flask were then boiled for a further 5 minutes, and the sulphuric acid neutralised by addition of sodium carbonate. The sludge was removed by filtration, and distillation of the filtrate afforded three fractions: (i) b. p. 110—130°, unchanged chlorohydrin mixed with a small amount of dioxan, (ii) b. p. 80—110°/15 mm., the crude dichlorohydrin, and (iii) b. p. 110—150°/15 mm., presumably a mixture of higher homologues. The diethylene chlorohydrin was freed from traces of ethylene glycol by washing with an equal volume of water, extracting with ether, drying (Na_2SO_4), and fractionally distilling. The pure compound had b. p. 85—93°/10 mm., 92—100°/15 mm. (Found: Cl, 28·3; OH, 13·9. Calc. for $C_4H_9O_2Cl$: Cl, 28·5; OH, 13·7%).

2-Hydroxy-2′-mercaptodiethyl Ether (V) *and 2 : 2′-Di-(2-hydroxyethoxy)diethyl Sulphide* (II).—Sodium (23 g.) was dissolved in absolute alcohol (500 c.c.), and the solution saturated with hydrogen sulphide and left overnight with a slow stream of hydrogen sulphide passing through. The stream of gas was continued both whilst diethylene chlorohydrin (125 g.) was added during ½ hour and also during the subsequent heating of the mixture to 50° for 30 minutes and to the b. p. for a further 30 minutes. The precipitated salt was then filtered off, the alcoholic solution made slightly acid with concentrated hydrochloric acid, the alcohol removed, and the product distilled. The crude *ether* (V) first distilled, b. p. 78—80°/1 mm. (Found: SH, 26·0. $C_4H_{10}O_2S$ requires SH, 27·0%), followed by the *sulphide* (II), b. p. 180°/1·5 mm. (Found: S, 16·0. $C_8H_{18}O_4S$ requires S, 15·3%).

1 : 17-*Dichloro*-6 : 12-*dioxa*-3 : 9 : 15-*trithiaheptadecane* (I, $n = 2$).—The foregoing sulphide (50 g.) was dissolved in dry chloroform (200 c.c.), and pure thionyl chloride (40 c.c.) run in rapidly. After standing for 30 minutes, the mixture was heated on the water-bath for 10 minutes, and the chloroform and unchanged thionyl chloride then removed in a vacuum at 30°. On distillation, impure 2 : 2′-*di-(2-chloroethoxy)diethyl sulphide* (III), b. p. 145°/1 mm., was obtained in 50% yield (Found: Cl, 29·0; S, 14·0. $C_8H_{16}O_2Cl_2S$ requires Cl, 28·4; S, 13·0%). The chloro-sulphide (10 g.) was added to a solution of 2-hydroxyethanethiol (6·3 g.) in sodium ethoxide (1·8 g. of sodium) and boiled for ½ hour on the water-bath. The precipitated salt was filtered off, and removal of the alcohol left the *sulphide* (IV) as a pale yellow oil solidifying on cooling; needles, m. p. 48—49°, from ether. The *α-naphthylurethane* formed needles, m. p. 83°, from ethyl acetate–petrol (Found: S, 14·1. $C_{34}H_{40}O_6N_2S_3$ requires S, 14·4%). Conversion into the *chloro*-compound (I; $n = 2$) with thionyl chloride was effected in the normal manner. Extraction of the product with boiling light petroleum (b. p. 40—60°) and cooling in ice gave needle rosettes, m. p. 18°, which were filtered off on a cold filter (Found: Cl, 19·4; S, 26·4. $C_{12}H_{24}O_2Cl_2S_3$ requires Cl, 19·1; S, 26·2%). The *bis(methylthio)-ether*, m. p. 42°, was obtained either by interaction of the chloro-sulphide with 10% excess of the sodium mercaptide of (III) with methyl 2-mercaptoethyl sulphide in the requisite amount of sodium ethoxide (Found: S, 40·5. $C_{14}H_{30}O_2S_5$ requires S, 41·0%); the *dithiophenoxide*, needle rosettes, had m. p. 44° from ethyl acetate–alcohol (Found: S, 31·2. $C_{24}H_{34}O_2S_5$ requires S, 31·1%).

1 : 23-*Dichloro*-6 : 12 : 18-*trioxa*-3 : 9 : 15 : 21-*tetrathiatricosane* (I; $n = 3$).—Dichlorodiethyl ether (29·3 g.) was added rapidly to a solution of 2-hydroxy-2′-mercaptodiethyl ether (50 g.) in sodium ethoxide (9·5 g. of sodium). The mixture was kept for ½ hour and then heated for a futher ½ hour on the water-bath, filtered from salt, and the alcohol removed. On distillation of the residual oil, the *com-*

pound (VI), b. p. 230°/1 mm., was obtained as a colourless viscous oil (Found: S, 20·7. $C_{12}H_{26}O_3S_2$ requires S, 20·4%). The pyridine–acetic anhydride method of estimating hydroxyl groups was inapplicable to this and analogous compounds. Conversion into the *chloro*-compound (VII) was carried out in the normal manner, thionyl chloride being used. It could not be distilled without decomposition at 1 mm. (b. p. 200—210°) but distilled smoothly at 125—130°/0·02 mm. (Found: Cl, 21·0; S, 17·2. $C_{12}H_{24}O_2Cl_2S_2$ requires Cl, 20·2; S, 17·2%). The chloro-compound (10 g.) was added rapidly to a solution of 2-hydroxyethanethiol (5 g.) in sodium ethoxide (1·3 g. of sodium) and heated for ½ hour on the water-bath. The precipitated salt was filtered off and the alcohol removed to leave 1 : 23-dihydroxy-6 : 12 : 18-trioxa-3 : 9 : 15 : 21-tetrathiatricosane (VIII) as a pale yellow oil which solidified on cooling; needles, m. p. 58—58·5°, from ether; *α-naphthylurethane*, needles, m. p. 69°, from ethyl acetate–light petroleum (Found: S, 16·6. $C_{38}H_{48}O_7N_2S_4$ requires S, 16·6%). The method of conversion into the *chloro*-compound (I; $n = 3$) and the isolation procedure were identical with those employed in the synthesis of the lower analogue (I; $n = 2$). It was obtained as needle rosettes, m. p. 28·5°, from ethyl acetate–alcohol (Found: Cl, 15·5; S, 27·6. $C_{16}H_{32}O_3Cl_2S_4$ requires Cl, 15·1; S, 27·2%). The *bismethylthioether* was obtained as needle rosettes, m. p. 45°, from ethyl acetate–alcohol (Found: S, 39·1. $C_{18}H_{38}O_3S_6$ requires S, 38·9%), and the *dithiophenoxide*, m. p. 50°, was similarly obtained (Found: S, 30·6. $C_{28}H_{42}O_3S_6$ requires S, 31·1%).

1 : 23-*Dihydroxy*-3 : 9 : 15 : 21-*tetraoxa*-6 : 12 : 18-*trithiatricosane*.—2 : 2-Di-(2-chlorethoxy)diethyl sulphide (10 g.) was added to a solution of 2-hydroxy-2′-mercaptodiethyl ether (10·4 g.) in sodium ethoxide (2 g. of sodium) and heated on the water-bath for one hour. The precipitated salt was filtered off and the solvent removed, leaving a pale yellow oil which solidified on cooling to 0°. Distillation of this oil gave a colourless solid, b. p. 230°/0·01 mm., m. p. 19°. An attempt to convert this into the chloro-compound under conditions similar to those employed in the preparation of the analogous (VII) failed, as a dark red oil which would not solidify and decomposed on distillation was formed. Condensation of this crude chloro-compound with 2-hydroxyethanethiol failed to give the desired dihydroxy-compound corresponding to (I; $n = 4$).

2-*Mercapto*-2′-(2-*hydroxyethylthio*)*diethyl Ether* (IX).—Ethylene chlorohydrin (80·5 g.) was added gradually to a solution of 2 : 2′-dimercaptodiethyl ether (138 g.) in sodium ethoxide (23 g. of sodium). After the reaction had subsided, the mixture was heated on the water-bath for ½ hour, filtered from salt, and the alcohol removed. Distillation of the product gave, besides unreacted ether, the required 2-*mercapto*-2′-(2-*hydroxyethylthio*)*diethyl ether*, b. p. 60°/1·5 mm., in 40% yield (Found: SH, 18·1. $C_6H_{14}O_2S_2$ requires SH, 18·1%), and 2 : 2′-di-(2-hydroxyethylthio)diethyl ether (30% yield), identified by mixed m. p. with an authentic specimen, m. p. 29—30°.

1 : 29-*Dichloro*-6 : 12 : 18 : 24-*tetraoxa*-3 : 9 : 15 : 21 : 27-*pentathianonacosane* (I, $n = 4$).—2 : 2′-Di-(2-chlorethoxy)diethyl sulphide (6·8 g.) was added to a solution of 2-mercapto-2′-(2-hydroxyethylthio)diethyl ether (10 g.) in sodium ethoxide (1·25 g. of sodium) and heated on the water-bath for one hour. The precipitated salt was filtered off, and the solution left to crystallise, the pentathiodiglycol being obtained as needles from alcohol, m. p. 60—61°; *α-naphthylurethane*, needles from ethyl acetate–light petroleum, m. p. 73—74° (Found: S, 18·3. $C_{43}H_{56}O_8N_2S_8$ requires S, 18·3%). Thionyl chloride (3 c.c.) was added to the pentathiodiglycol (5 g.) in chloroform (40 c.c.), and by employing the procedure used in the preparation of (I; $n = 2$), the *compound* (I, $n = 4$) was obtained as needle rosettes, m. p. 32—33°, from ethyl acetate–alcohol (Found: Cl, 12·2; S, 28·3. $C_{20}H_{40}O_4Cl_2S_5$ requires Cl, 12·3; S, 27·8%); *dithiophenoxide*, needle rosettes, m. p. 55°, from ethyl acetate–alcohol (Found: S, 31·1. $C_{32}H_{50}O_4S_7$ requires S, 31·0%).

1 : 35-*Dichloro*-6 : 12 : 18 : 24 : 30-*pentaoxa*-3 : 9 : 15 : 21 : 27 : 33-*hexathiapentatriacontane* (I, $n = 5$).—The ether (VII, 9 g.) was added to a solution of 2-mercapto-2′-(2-hydroxyethylthio)diethyl ether (10 g.) and sodium ethoxide (1·25 g. of sodium), and heated on the water-bath for one hour. After removal of the precipitated salt the hexathiodiglycol crystallised and was obtained as needles, m. p. 62·5°, from alcohol; *α-naphthylurethane*, needles, m. p. 79°, from ethyl acetate–light petroleum (Found: S, 19·4. $C_{46}H_{64}O_8N_2S_6$ requires S, 19·6%). Interaction of the hexathiodiglycol (10 g.) with thionyl chloride (4 c.c.) in chloroform (70 c.c.) gave the desired *chloro*-compound as needle rosettes, m. p. 37° from ethyl acetate (Found: Cl, 10·2; S, 29·0. $C_{24}H_{48}O_5Cl_2S_6$ requires Cl, 10·5; S, 28·3%); *dithiophenoxide*, needle rosettes, m. p. 57°, from ethyl acetate–alcohol (Found: S, 30·8. $C_{36}H_{56}O_5S_8$ requires S, 31·0%).

Most of the analyses were carried out by, or under the direction of, Mr. A. Wright. Thanks are due to the Chief Scientist, Ministry of Supply, for permission to publish these results.

H.M. Research Establishment, Sutton Oak. [*Received, January 9th*, 1947.]

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10. *New Organic Sulphur Vesicants. Part IV.* 1 : 2-*Di*-(2-*chloroethylthio*)*ethane and its Analogues.*

By E. J. Gasson, H. McCombie, A. H. Williams, and F. N. Woodward.

The powerful vesicant 1 : 2-di-(2-chloroethylthio)ethane, the third member of the homologous series having the general formula (I), has been obtained in admixture with (II) by the action of hydrogen chloride on a mixture of thiodiglycol and 2-hydroxyethanethiol (III). With initial concentrations of (III) greater than 10%, condensation compounds of the general formula (IV) are obtained in addition.

Homologues (I; $n = 0$, 1, 3, 4, 5, 6, 8, 9 and 10) have also been synthesised, all of which, except the last three, are vesicant to man. 1 : 2-Di-(2-chloro-*n*-propylthio)ethane has also been prepared.

1 : 2-Di-(2-chloroethylthio)ethane (" sesqui-H "; Q) (I; $n = 2$), the third member of the homologous series having the general formula (I), has vesicant power approximately five times that of 2 : 2′-dichlorodiethyl sulphide (II) (mustard gas; H). It was first obtained by Bennett *et al.* (*J.*, 1921, **119**, 1860; 1922, **121**, 2146) by the action of thionyl chloride on the corresponding hydroxy-compound, prepared by interaction of ethylene dibromide and 2-hydroxyethanethiol (III) in alcoholic sodium ethoxide. Rosen and Reid (*J. Amer. Chem. Soc.*, 1922, **44**, 634) confirmed its structure by synthesis from ethane-1 : 2-dithiol and ethylene chlorohydrin.

(I.) $Cl{\cdot}C_2H_4{\cdot}S{\cdot}[CH_2]_n{\cdot}S{\cdot}C_2H_4Cl$ $Cl{\cdot}CH_2{\cdot}CH_2{\cdot}S{\cdot}CH_2{\cdot}CH_2Cl$ (II.)

The compound (I; $n = 2$) has now been prepared, together with (II), by the action of hydrogen chloride on a mixture of (III) and 2 : 2′-dihydroxydiethyl sulphide (thiodiglycol) at 90° :

$$S(C_2H_4{\cdot}OH)_2 + \underset{\text{(III.)}}{HS{\cdot}C_2H_4{\cdot}OH} \xrightarrow{HCl} (I;\ n = 2) + 3H_2O$$

With less than 10% of (III) in the initial reaction mixture a product is obtained which, when freed from (II) by distillation under reduced pressure, is essentially pure (I; $n = 2$). With higher initial concentrations, further condensation occurs :

$$S(C_2H_4{\cdot}OH)_2 \longrightarrow \{HO{\cdot}[C_2H_4{\cdot}S]_n{\cdot}C_2H_4{\cdot}OH\} \xrightarrow{HCl + (III)} Cl{\cdot}[C_2H_4{\cdot}S]_n{\cdot}C_2H_4Cl \quad \text{(IV.)}$$

From the condensation products obtained, (IV; $n = 3$) and (IV; $n = 5$) have been isolated.

The preparations of (I; $n = 0$, 1, 3, and 4) have also been described previously, but as in some cases the purity of the compounds obtained was open to doubt, these preparations have been repeated. In addition, *compounds* (I), where $n = 5$, 6, 8, 9, and 10, have been prepared. With the exception of (I; $n = 0$), all nine compounds were obtained by the general reactions :

$$X{\cdot}[CH_2]_n{\cdot}X \xrightarrow{(III) + NaOEt} [CH_2]_n[S{\cdot}C_2H_4{\cdot}OH]_2 \xrightarrow{SOCl_2} [CH_2]_n(S{\cdot}C_2H_4Cl)_2$$

The hydroxy-precursor of the first compound of the series was obtained by oxidation of (III) with hydrogen peroxide.

The empirical vesicant powers of these compounds (compared with H = 100) were assessed by the Physiological Section, Chemical Defence Experimental Station, Porton. The method of expressing physiological activity is the same as in Part II. Table I gives details of the compounds prepared and tested.

TABLE I.

M. p., b. p., and empirical vesicant powers of compounds of the series $[CH_2]_n(S{\cdot}C_2H_4X)_2$.

	X = OH.		X = Cl.		Empirical vesicant power (H = 100).
n.	B. p.	M. p.	B. p.	M. p.	
0	106°/0·015 mm.	25—26°	100°/0·5 mm., 150/30 mm. (*a*)	−2° to 0°	1
1	114—115/0·005 mm., 200—203/17 mm. (*b*)	18	80—81/0·03 mm.	30·7, <−27 (*b*)	200
2	—	—	*ca.* 140/2 mm.	57	500
		64 (*c*)		54 (*c*)	
		117 (*d*)		64 (*d*)	
3	200/4 mm.; 89—90/0·003 mm.	18	86/0·04 mm.	11·5	400—500
	230—233/17 mm. (*b*)	—	200—204/17 mm. (*b*)	liquid (*b*)	
4	207/3 mm.	30	104/0·06 mm.	−1	400
		27—29 (*e*)		<−20 (*e*)	
5	210/3 mm.	30	104/0·003 mm.	−6	200
6	*ca.* 130/0·02 mm.	45	112/0·03 mm.	14—15	50
8	—	60—61 (*f*)	134/0·045 mm.	21—22	1
9	—	63—64 (*f*)	—	24 (*h*)	1
10	—	70 (*g*)	—	32 (*h*)	1

(*a*) Bennett, *J.*, 1921, **119**, 424.
(*b*) Alexander, Ph.D. Thesis, 1933, Cambridge.
(*c*) Bennett and Whincop, *J.*, 1921, **119**, 1860.
(*d*) Rosen and Reid, *loc. cit.*
(*e*) Kent and McCombie; unpublished work.
(*f*) Crystallised from ethyl acetate–light petroleum.
(*g*) Crystallised from ethyl acetate.
(*h*) Crystallised from methanol–chloroform.

1 : 2-*Di*-(2-*hydroxy*-n-*propylthio*)*ethane* has been obtained by the interaction of (II) and 2-hydroxypropanethiol in alcoholic sodium ethoxide. The corresponding ***chloro*-compound** (empirical vesicant power = 50) is obtained by interaction with thionyl chloride.

Experimental.

Condensation of Thiodiglycol and 2-Hydroxyethanethiol.—The thioglycols (100 g. total) were well mixed in the required proportion (see below) in a 2-l. round-bottomed flask and heated under reflux with concentrated hydrochloric acid (400 c.c.) for 75 minutes at 90°. After cooling of the reaction product, the lower non-aqueous layer was separated and the 2 : 2′-dichlorodiethyl sulphide (II) removed by distillation at 2·5 mm., leaving the crude substance (I; $n = 2$) as an undistillable residue. Mixed glycol and thiol in the following respective proportions by weight were condensed.

90 : 10. The product (122·5 g.) was a pale yellow liquid, s. p. 8°. On distillation it gave (II) (80·8%), m. p. 13·5°, as distillate and a residue of crude (I; $n = 2$) (19·2%), m. p. 51° after softening at 48—49°. Bennett and Whincop (*loc. cit.*) give m. p. 54° (Found: S, 29·6; Cl, 32·1. Calc. for $C_6H_{12}S_2Cl_2$: S, 29·3; Cl, 32·4%).

80 : 20. The product (115 g.), m. p. 5°, on distillation gave (II) (69·0%), m. p. 13·6°, and a residue, m. p. 47°, finally clearing at 61° (Found: S, 30·9; Cl, 30·3%).

70 : 30. At room temperature the product (98·7 g.) deposited a white crystalline solid (40 g.). Distillation afforded (II) (54·6%), m. p. 13·3°, and the residue (45·4%) had m. p. 60—65° (Found: S, 33·7; Cl, 27·3%). This and the residue described above are presumably mixtures of (IV; $n = 2$ and 3) (Calc. for $C_8H_{16}S_3Cl_2$: S, 34·4; Cl, 25·4%).

61 : 39 (equimolar). The non-aqueous layer (106 g.) was separated at 70°, below which temperature crystals began to separate. Distillation yielded (II) (46·0%), m. p. 12°, and a residue (54·0%) melting between 68° and 75°. This on fractional crystallisation from alcohol–chloroform gave crude (I; $n = 2$) (20·6 g.), m. p. 57—59°, a mixed fraction (12 g.), m. p. 45—51° (Found: S, 32·4; Cl, 23·8%), and 1 : 17-*dichloro*-3 : 6 : 9 : 12 : 15-*pentathiaheptadecane* (IV; $n = 5$), an amorphous solid, m. p. 100° (Found: S, 40·2; Cl, 17·5; *M*, cryoscopic in $CHBr_3$, 362. $C_{12}H_{24}S_5Cl_2$ requires S, 40·1; Cl, 17·8%; *M*, 399).

Synthesis of Compounds of the Series $[CH_2]_n(S{\cdot}C_2H_4X)_2$.—With the exception of the first compound ($n = 0$), the method described in Part II for the synthesis of 2 : 2′-di-(2-chloroethylthio)diethyl sulphide was employed throughout. In all cases purification was effected by distillation in a vacuum. The highest homologues and their hydroxy-precursors were also purified by crystallisation. The analytical data are given in Table II.

Table II.

	X = OH.			X = Cl.				
		S, %.			Found, %.		Calc., %.	
n.	Formula.	Found.	Calc.	Formula.	Cl.	S.	Cl.	S.
0	$C_4H_{10}O_2S_2$	41·6	41·6	$C_4H_8Cl_2S_2$	35·3 (*a*)	34·1	37·2	33·5
1	—	—	—	$C_5H_{10}Cl_2S_2$	34·6	31·8	34·6	31·2
3	$C_7H_{16}O_2S_2$	32·2	32·6	$C_7H_{14}Cl_2S_2$	30·1	—	30·1	—
4	$C_8H_{18}O_2S_2$	30·1	30·5	$C_8H_{16}Cl_2S_2$	28·5	—	28·7	—
5	$C_9H_{20}O_2S_2$	28·3	28·5	$C_9H_{18}Cl_2S_2$	27·3	—	27·2	—
8	$C_{12}H_{26}O_2S_2$	24·1	24·1	$C_{12}H_{24}Cl_2S_2$	23·1	20·9	23·4	21·1
9	$C_{13}H_{28}O_2S_2$	23·2	22·9	$C_{13}H_{26}Cl_2S_2$	22·4 *	21·7 *	22·4	20·2
10	$C_{14}H_{30}O_2S_2$	22·1	21·8	$C_{14}H_{28}Cl_2S_2$	22·0	19·3	21·5	19·3

(*a*) Cf. Bennett (*loc. cit.*) for similar low Cl result.

Except with di-(2-chloroethylthio)methane, where methylene chloride was used, alkylene dibromides were employed as starting materials in each case. 1 : 6-Dibromohexane was obtained in 50% yield by refluxing hexane-1 : 6-diol (Muller and Sauerwald, *Monatsh.*, 1927, **48**, 521) with constant-boiling hydrobromic acid in the presence of a trace of concentrated sulphuric acid. The octane-, nonane-, and decane-diols were obtained from ethyl suberate (52% yield), azelate (64% yield), and sebacate (75% yield), respectively, by Bouveault–Blanc reduction and the technique of Bennett and Mosses (*J.*, 1931, 1697). Conversion into the $\alpha\omega$-dibromides was effected by the action of dry gaseous hydrogen bromide on the molten diols at *ca.* 130° (cf. Carothers, *J. Amer. Chem. Soc.*, 1930, **52**, 5279). Yields obtained were: 1 : 8-dibromo-octane, b. p. 116°/3 mm., 86%; 1 : 9-dibromononane, b. p. 120°/3 mm., 80%; 1 : 10-dibromodecane, b. p. 138°/4 mm., m. p. 27°, 73%. 1 : 2-Di-(2-chloro-*n*-propylthio)ethane was similarly obtained from ethylene dibromide and 2-hydroxypropanethiol. The intermediate 1 : 2-*di*-(2-*hydroxy*-n-*propylthio*)*ethane* was obtained as a wax, b. p. 189—190°/5 mm., m. p. 28° (Found: S, 30·6; OH, 16·0. $C_8H_{18}O_2S_3$ requires S, 30·5; OH, 16·0%). The *chloro*-compound had b. p. 78—79°/0·005 mm., m. p. 14—15° (Found: Cl, 28·4. $C_8H_{16}Cl_2S_2$ requires Cl, 28·7%).

Di-(2-chloroethyl) Disulphide.—2-Hydroxyethanethiol (60 g.) was oxidised by careful addition of 30·5% w/v hydrogen peroxide (43 c.c.), the temperature being kept below 50°. After removal of the water under low pressure, a thick colourless syrup remained which could not be induced to crystallise, but could be distilled in small batches, if done quickly. The pure *dihydroxy-disulphide* was obtained as a white solid, b. p. 106°/0·015 mm., m. p. 25—26° (Found: S, 41·6. $C_4H_{10}O_2S_2$ requires S, 41·6%). Conversion into the chloro-compound by means of thionyl chloride was effected in the usual manner.

Microanalyses marked * were carried out by Mr. G. Ingram; other analyses were done by, or under the direction of, Mr. A. Wright.

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11. *New Organic Sulphur Vesicants. Part V. 2-Chloroethyl 2-Chloroisopropyl Sulphide.*

By A. Hamilton, (the late) R. C. G. Moggridge, and F. N. Woodward.

The synthesis of the three diol isomers (I; X = OH), (II), and 2-hydroxyethyl 2-hydroxy-*n*-propyl sulphide from 2-hydroxyethanethiol and allyl alcohol, trimethylene chlorohydrin, and 1-chloro-2-hydroxypropane, respectively, is described. Conversion of (I; X = OH) into (I; X = Cl) is effected by concentrated hydrochloric acid.

2-Chloroethyl 2-chloro*iso*propyl sulphide (I; X = Cl) was prepared by Williams and Woodward (see Part II), who obtained the related diol (I; X = OH) by reduction of 1-(2-hydroxyethylthio)propaldehyde. This synthesis of (I; X = Cl) involved five stages and

$$X{\cdot}C_2H_4{\cdot}S{\cdot}CHMe{\cdot}CH_2X \quad (I.) \qquad HO{\cdot}C_2H_4{\cdot}S{\cdot}CH_2{\cdot}CH_2{\cdot}CH_2{\cdot}OH \quad (II.)$$

gave an overall yield of only 8%. A more direct synthesis has now been found in that (I; X = OH) is prepared by addition of 2-hydroxyethanethiol to allyl alcohol. In the absence of a catalyst these compounds interact to give the "abnormal" *product* (II); this behaviour is apparently general for thiol–olefin additions (cf., *inter alia*, Kharasch, Read, and Mayo, *Chem. and Ind.*, 1938, **16**, 752; Ipatieff, Pines, and Friedman, *J. Amer. Chem. Soc.*, 1938, **60**, 2371; Jones and Reid, *ibid.*, p. 2452; Ipatieff and Friedman, *ibid.*, 1939, **61**, 71). The constitution of (II) was confirmed by synthesis from 2-hydroxyethanethiol and 1 : 3-propylenechlorohydrin.

If, however, 2-hydroxyethanethiol and allyl alcohol were heated together in presence of sulphur (Jones and Reid, *loc. cit.*), the "normal" product (I; X = OH) was obtained in 55—60% yield. It could be converted into (I; X = Cl) by the action of concentrated hydrochloric acid at 80—90°, the overall yield then being *ca.* 40%.

A third diol isomer, *viz.*, 2-hydroxyethyl 2-hydroxy-*n*-propyl sulphide has now been prepared from 2-hydroxyethanethiol and 1-chloro-2-hydroxypropane (cf. E.P. 185,402; *Chem. Zentr.*, 1923, II, 684, in which is described the preparation, but not the characterisation, of this compound).

Experimental.

*2-Hydroxyethyl 3-Hydroxy-*n*-propyl Sulphide* (II).—(*a*) Allyl alcohol and 2-hydroxyethanethiol (Bennett, *J.*, 1921, **119**, 423) were mixed in equimolecular proportion and heated under reflux for 3 hours. Distillation of the mixture gave the *diol* (II) in 50% yield, as a colourless oil, b. p. 144°/2·5 mm. (Found: S, 23·3; OH, 24·55. $C_5H_{12}O_2S$ requires S, 23·45; OH, 25·0%); *bis*-p-*nitrobenzoate*, colourless prisms, m. p. 110°, from alcohol (Found: C, 52·1; H, 3·4; N, 6·5. $C_{19}H_{18}O_8N_2S$ requires C, 52·5; H, 4·2; N, 6·45%).

(*b*) Trimethylene chlorohydrin (*Org. Synth.*, **8**, 112) (0·5 g.-mol.) was added to 2-hydroxyethanethiol (0·5 g.-mol.) in sodium ethoxide solution (250 c.c.; 2N), reaction occurring with evolution of heat. The product, isolated by removal of sodium chloride, concentration, and distillation, boiled at 141—146°/2 mm. (Found: S, 23·3%); bis-*p*-nitrobenzoate, m. p. 110°, identical (mixed m. p.) with that obtained as above.

2-Hydroxyethyl 2-Hydroxyisopropyl Sulphide (I; X = OH).—Allyl alcohol (29 g.), 2-hydroxyethanethiol (39 g.), and sulphur (0·5 g.) were mixed and heated under reflux for 6 hours; on distillation of the mixture the required diol (II) was obtained in 55—60% yield as a colourless oil, b. p. 136—137°/5 mm.; the *bis*-p-*nitrobenzoate*, needles from alcohol, m. p. 113° (Found: C, 52·65; H, 4·5; N, 6·60. $C_{19}H_{18}O_8N_2S$ requires C, 52·5; H, 4·2; N, 6·45%), was identical (mixed m. p.) with that of the diol (I; X = OH), prepared by the method of Williams and Woodward, and showed marked depression of m. p. when mixed with the bis-*p*-nitrobenzoate of (II).

2-Chloroethyl 2-Chloroisopropyl Sulphide (I; X = Cl).—Either the distilled diol (I; X = OH) or the crude reaction product was treated with concentrated hydrochloric acid (10 vols.) at 80—90° for one hour with occasional shaking. The product separated as a heavy oil, b. p. 69—71°/2 mm., 79—81°/5 mm., overall yield (from 2-hydroxyethanethiol) *ca.* 40%, whether crude or pure (I; X = OH) was used (Found: S, 18·6; Cl, 40·55. Calc. for $C_5H_{10}Cl_2S$: S, 18·5; Cl, 41·0%); tribromophenoxide, m. p. 128° (Found: S, 4·15; Br, 62·85. Calc. for $C_{17}H_{14}O_2SBr_6$: S, 4·2; Br, 63·0%).

*2-Hydroxyethyl 2-Hydroxy-*n*-propyl Sulphide.*—1-Chloro-2-hydroxypropane (10·2 g.) was added to 2-hydroxyethanethiol (8·6 g.) in a solution of sodium ethoxide (1 equiv.) in alcohol, reaction occurring with evolution of heat. The *product*, isolated by removal of sodium chloride and solvent, had b. p. 120—125°/2·5 mm. (Found: S, 23·6; OH, 24·65. $C_5H_{12}O_2S$ requires S, 23·5; OH, 25·0%); *bis*-p-*nitrobenzoate*, m. p. 85° (Found: S, 7·5. $C_{19}H_{18}O_8N_2S$ requires S, 7·4%).

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12. *The Synthesis of* 2-cyclo*Hexyl*-6-*methylheptane.*

By D. H. Hey and D. S. Morris.

2-cyclo*Hexyl*-6-*methylheptane* has been prepared by the catalytic reduction of 2-*phenyl*-6-*methylhept*-2-*ene*, which was obtained from the action of phenylmagnesium bromide on methylheptanone. The action of *cyclo*hexylmagnesium halides on methylheptanone appears to result in the self-condensation of the ketone. *cyclo*Hexylmagnesium halides effect the self-condensation of ethyl phenylacetate to give ethyl αγ-diphenylacetoacetate; the action of bromine on the latter gives *αγ-diphenyltetronic acid*.

2-cyclo*Hexyl*-6-*methylheptane* (III, R = *cyclo*hexyl) has been prepared from 6-methylheptan-2-one, which reacted with phenylmagnesium bromide to give *phenylmethylisohexylcarbinol* (I); dehydration of this with formic acid gave an unsaturated hydrocarbon regarded as 2-*phenyl*-6-*methylhept*-2-*ene* (II), which was catalytically reduced at room temperature and pressure to 2-*phenyl*-6-*methylheptane* (III, R = C_6H_5). The further catalytic reduction of the latter under more drastic conditions gave 2-*cyclo*hexyl-6-methylheptane (III, R = *cyclo*hexyl).

$$CH_3\cdot\overset{\overset{OH}{|}}{C}(C_6H_5)\cdot[CH_2]_3\cdot CH(CH_3)_2 \longrightarrow CH_3\cdot C(C_6H_5)=CH\cdot[CH_2]_3\cdot CH(CH_3)_2 \longrightarrow CH_3\cdot\overset{\overset{R}{|}}{C}H\cdot[CH_2]_3\cdot CH(CH_3)_2$$

(I.) (II.) (III.)

The pure 6-methylheptan-2-one required in the above work was prepared by the method of Verley (*Bull. Soc. chim.*, 1899, **17**, 176), whereby methylheptenone, obtained from citral by boiling under reflux with aqueous sodium carbonate, is hydrogenated to the saturated ketone (cf. Wallach, *Annalen*, 1911, **381**, 86). It was not found practicable to obtain the pure ketone in quantity by the method of Clarke (*J. Amer. Chem. Soc.*, 1909, **31**, 107), using *iso*amyl halides and the sodium derivative of ethyl acetoacetate followed by ketonic hydrolysis. The ketone obtained by this method showed the correct boiling point, but invariably gave derivatives having low melting points, thus indicating the presence of mixtures. This is probably due to the presence of isomerides in the *iso*amyl alcohol used as one of the starting materials. Although Clarke claimed it to be unnecessary to purify the alcohol it is significant that he did not report the preparation of any ketonic derivatives in order to establish the purity of his product. It was found that pure methylheptanone could be obtained by this method only after a tedious fractional crystallisation of the semicarbazone followed by hydrolysis.

Attempts to obtain 2-*cyclo*hexyl-6-methylheptane by the direct action of *cyclo*hexylmagnesium chloride on methylheptanone, followed by dehydration and hydrogenation of the double bond, were unsuccessful, since the Grignard reagent appeared to bring about self-condensation of the methylheptanone. Hickinbottom and Schlüchterer (*Nature*, 1945, **155**, 19) have recently drawn attention to the fact that certain Grignard reagents, such as *tert.*-butylmagnesium chloride, ethylmagnesium bromide, and phenylmagnesium bromide, will effect the self-condensation of methyl *tert.*-butyl ketone. More recently Shine and Turner (*Nature*, 1946, **158**, 170) have reported the formation of 2 : 4 : 8-trimethylnon-4-en-6-one from *iso*propylmagnesium bromide and methyl *iso*butyl ketone. *iso*Propylmagnesium bromide readily effects the self-condensation of ethyl phenylacetate and ethyl *p*-chlorophenylacetate (Conant and Blatt, *J. Amer. Chem. Soc.*, 1929, **51**, 1227; Ivanov and Spasov, *Bull. Soc. chim.*, 1931, **49**, 375). It is now shown that *cyclo*hexylmagnesium halides will also bring about the self-condensation of ethyl phenylacetate to give ethyl αγ-diphenylacetoacetate in good yield. Before the identity of the latter compound was known it was subjected to the action of bromine in glacial acetic acid solution. In the resulting reaction hydrogen bromide was evolved and a crystalline acidic product was obtained. Dimroth and Eble (*Ber.*, 1906, **39**, 3928) have reported the isolation of α-phenyltetronic acid from the product of the action of bromine on ethyl α-phenylacetoacetate and, by analogy, the above-mentioned acidic product is regarded as *αγ-diphenyltetronic acid*, which is in agreement with the analytical figures.

Experimental.

6-*Methylheptan*-2-*one*.—(a) *From citral.* Using the conditions given by Verley (*loc. cit.*), citral (250 g.) was boiled under reflux with 10% aqueous potassium carbonate (2,500 c.c.) for 12 hours and subsequently distilled with steam. The methylheptanone was extracted from the distillate, dried, and distilled (120 g., b. p. 80—84°/26 mm.; semicarbazone, m. p. 135—136°). After hydrogenation at room temperature and pressure in presence of platinum oxide catalyst and subsequent distillation through a 12-inch Fenske column, methylheptanone was obtained (92 g., b. p. 164—164·5°/757 mm., $n_D^{19°}$ 1·4144; semicarbazone, m. p. 154—155°; 2 : 4-dinitrophenylhydrazone, m. p. 77°).

(b) *From ethyl* iso*amylacetoacetate.* *iso*Amyl alcohol was fractionally distilled with a 12-inch Dufton column and the fraction, b. p. 130—131°/763 mm., collected. This fraction was converted into the iodide by the method of Clarke (*loc. cit.*), into the bromide using either phosphorus tribromide (*Org. Synth.*, 1933, **13**, 20) or hydrobromic acid and sulphuric acid (*ibid.*, Coll. Vol. I, 27), and into the chloride by the method of Whitmore, Karnatz, and Popkin (*J. Amer. Chem. Soc.*, 1938, **60**, 2540). The three halides were separately treated with ethyl acetoacetate and sodium by the method of Conrad and Limpach (*Annalen*, 1878, **192**, 153). The chloride did not react but the bromide and iodide gave crude ethyl *iso*amylacetoacetate in good yield (b. p. 117—119°/16 mm.). The esters thus obtained were treated with cold 5% aqueous sodium hydroxide and then acidified with 50% sulphuric acid (cf. *Org. Synth.*, Coll. Vol. I, 351). The crude ketones thus obtained were dried and fractionated twice with a 12-inch Fenske column. The final product had b. p. 165—165·5°/760 mm., $n_D^{19°}$ 1·4173 (Clarke, *loc. cit.*, records b. p. 165°, and Wallach, *loc. cit.*, $n_D^{19°}$ 1·4144), but the semicarbazone melted at 148—149° after repeated crystallisation (Wallach, *loc. cit.*, records m. p. 157—158°), and the 2 : 4-dinitrophenylhydrazone at 66—67° (Allen, *J. Amer. Chem. Soc.*, 1930, **52**, 2955, records m. p. 77°). The ketones were converted into semicarbazones, and fractional crystallisation from ethyl alcohol gave a product, m. p. 154—155°, both alone and on admixture with an authentic specimen prepared by method (a). The pure semicarbazone (63 g.) was hydrolysed by boiling it under reflux with a solution of oxalic acid (60 g.) in water (300 c.c.) for 30 minutes, and the liberated ketone was removed in steam. The resulting methylheptanone, which was obtained in almost quantitative yield, had the same constants as those recorded above for the product obtained by method (a).

*Phenylmethyliso**hexylcarbinol.*—Methylheptanone (30 g.) in ether (30 c.c.) was slowly added to a well-cooled solution of phenylmagnesium bromide, prepared from bromobenzene (74 g.), magnesium (11·4 g.), and ether (150 c.c.). The mixture was boiled gently under reflux for 4 hours and, after standing overnight, was worked up in the usual manner. The resulting oil was collected at 125—143°/7—10 mm. (46 g.), and on redistillation the *carbinol* was obtained as a colourless oil (36 g.), b. p. 128—132°/5 mm. (Found : C, 82·5; H, 10·3. $C_{14}H_{22}O$ requires C, 81·5; H, 10·7%).

2-Phenyl-6-methylhept-2-ene.—The carbinol (36 g.) was shaken with 98% formic acid (25 c.c.) and allowed to stand for 24 hours. The product was washed with water and with aqueous sodium carbonate. Distillation of the dried product gave *2-phenyl-6-methylhept-2-ene* (26·4 g.) as a colourless oil, b. p. 252—254°, $n_D^{16°}$ 1·5213 (Found : C, 89·3; H, 10·4. $C_{14}H_{20}$ requires C, 89·4; H, 10·6%). Oxidation with a warm solution of chromic anhydride in acetic acid gave acetophenone, identified as the 2 : 4-dinitrophenylhydrazone, m. p. and mixed m. p. 244—245°.

2-Phenyl-6-methylheptane.—The heptene (5·6 g.) in ethyl alcohol (25 c.c.) was hydrogenated at atmospheric pressure and temperature over platinum oxide (0·1 g.). After absorption of one molecular equivalent of hydrogen the product was distilled, and *2-phenyl-6-methylheptane* (4·9 g.) was collected as a colourless oil, b. p. 235—238°, $n_D^{16°}$ 1·4893 (Found : C, 88·4; H, 11·4. $C_{14}H_{22}$ requires C, 88·4; H, 11·6%).

2-cyclo*Hexyl-6-methylheptane.*—2-Phenyl-6-methylheptane (33 g.) in glacial acetic acid (250 c.c.) was hydrogenated over platinum oxide (2·5 g.) at 100° and 100—135 atmospheres for 24 hours. Distillation of the product gave 2-cyclo*hexyl-6-methylheptane* (30 g.) as a colourless liquid, b. p. 240—245°, $n_D^{17°}$ 1·4569 (Found : C, 85·5; H, 14·3. $C_{14}H_{28}$ requires C, 85·7; H, 14·3%).

Action of cyclo*Hexylmagnesium Chloride on Methylheptanone.*—A solution of methylheptanone (23 g.) in ether (25 c.c.) was slowly added to a well-cooled solution of *cyclo*hexylmagnesium chloride, prepared from *cyclo*hexyl chloride (23·7 g.), magnesium (5·35 g.), and ether (90 c.c.). The preparation of the Grignard reagent was found to be adversely affected to a marked degree by the presence of traces of aluminium in the magnesium. The solution was boiled under reflux for 30 minutes, and after standing overnight the product was worked up in the usual manner. An oil (36·7 g.) was obtained which boiled with some decomposition at 6 mm., but by distillation at 1 mm. the major fraction (22·1 g.) was collected at 125—128° as a colourless oil. Dehydration with 98% formic acid, as described above, gave a product, b. p. 50—80°/3—4 mm., which showed an equivalent of 120 on titration with pyridine sulphate dibromide, as described by Rosenmund (*Z. angew. Chem.*, 1924, **37**, 58). The equivalent for 2-*cyclo*hexyl-6-methylhept-2-ene is 97, and that for the condensation product resulting from two molecules of methylheptanone by loss of water is 119.

Action of cyclo*Hexylmagnesium Halides on Ethyl Phenylacetate.*—A solution of ethyl phenylacetate (13·5 g.) in ether (15 c.c.) was slowly added to a well-cooled solution of *cyclo*hexylmagnesium chloride, prepared from *cyclo*hexyl chloride (23·7 g.), magnesium (5·35 g.), and ether (90 c.c.). The mixture was boiled under reflux for 45 minutes and allowed to stand overnight. On working up in the usual manner, evaporation of the ether deposited ethyl *αγ*-diphenylacetoacetate as a crystalline solid (7·9 g., m. p. 71—72°), which crystallised from light petroleum (b. p. 40—60°)–benzene in colourless needles, m. p. 77—78° (Found : C, 76·8; H, 6·4. Calc. for $C_{18}H_{18}O_3$: C, 76·6; H, 6·4%). Conant and Blatt (*loc. cit.*) record m. p. 78° for ethyl *αγ*-diphenylacetoacetate. The same product was obtained when *cyclo*hexyl bromide was used in place of the chloride.

Action of Bromine on Ethyl αγ-Diphenylacetoacetate.—A solution of bromine (3·2 g.) in glacial acetic acid (20 c.c.) was added to a solution of the ester (5·7 g.) in the same solvent (70 c.c.). Hydrogen bromide was evolved and a crystalline deposit (4 g., m. p. 201—205°) separated on removal of most of the acetic acid under reduced pressure. The product was soluble in aqueous alkalis, but insoluble in acids. Recrystallisation from acetic acid gave *αγ-diphenyltetronic acid* in prisms, m. p. 204—205° [Found : C, 75·9; H, 4·8; equiv. (by silver salt), 253. $C_{16}H_{12}O_3$ requires C, 76·2; H, 4·8%; equiv., 252].

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13. *The Action of Hydrogen Peroxide on Symmetrical Triketones.*

By C. H. Hassall.

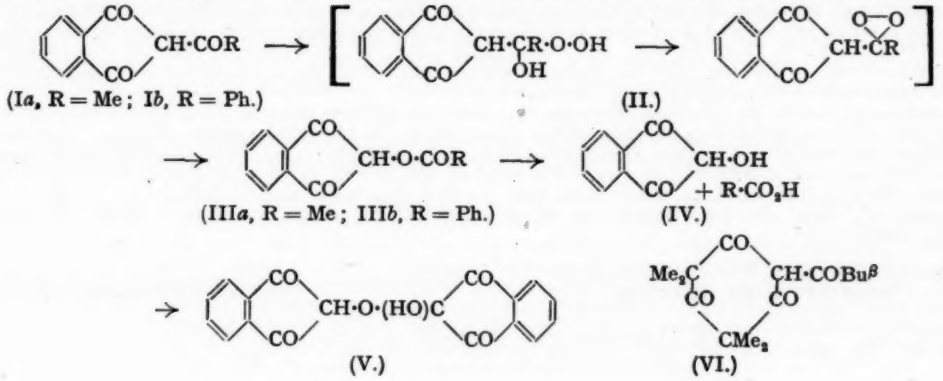
The oxidation of 1 : 3-diketo-2-acylindane and triacylmethane derivatives with hydrogen peroxide in acid, alkaline, and neutral media has been investigated.

In the course of investigations on leptospermone (Briggs, Hassall, and Short, *J.*, 1945, 706) it was shown that oxidation of this tetramethylphloroglucinol derivative (VI) with hydrogen peroxide resulted in specific attack on the acyl side chain with the formation of an ester. In view of the interest attached to compounds of natural occurrence and physiological activity containing the symmetrical triketone structure present in leptospermone (*Aspidium filix mas* derivatives : Boehm, *Annalen*, 1901, **318**, 230; diketoacylindanes : Kilgore, Ford, and Wolfe, *Ind. Eng. Chem.*, 1942, **34**, 494; protokosin : Hems and Todd, *J.*, 1937, 562; humulone and lupulone : Wollmer, *Ber.*, 1916, **49**, 780) and the possible application of this method of oxidation in further degradative studies on such structures, the reaction has been further investigated using diketoacylindane and triacylmethane derivatives as representative types.

In the concentrated sulphuric acid (Baeyer and Villiger, *Ber.*, 1900, **33**, 124; Ruzicka and Stoll, *Helv. Chim. Acta*, 1928, **11**, 1159) or alkaline (Dakin, *Amer. Chem. J.*, 1909, **42**, 474) solutions which have been applied in similar hydrogen peroxide oxidations, 1 : 3-diketo-2-acetyl- and 2-benzoyl-indane are degraded to phthalic acid and acetic and benzoic acids respectively. Perbenzoic acid (Burchhardt and Reichstein, *Helv. Chim. Acta*, 1942, **25**, 1434) and peracetic acid (Wacek and Bezard, *Ber.*, 1941, **74**, 845) had no action on the ketones. In ethereal solution hydrogen peroxide converted diketobenzoylindane into a compound $C_{16}H_{10}O_4$, which was identified as 1 : 3-*diketo*-2-*benzoyloxyindane* (III*b*), since on alkaline hydrolysis it gave 2-hydroxy-1 : 3-diketoindane (IV) and benzoic acid. The product (IV) was characterised by precipitation as hydrindantin (V) (Ruhemann, *J.*, 1911, **99**, 792) on treatment with aqueous triketoindane hydrate. Similar reactions occur with the product $C_{11}H_8O_4$ (III*a*) obtained on oxidation of 1 : 3-diketo-2-acetylindane under neutral conditions. In alkaline and sulphuric acid media (III*a*) and (III*b*) decompose to phthalic acid and the corresponding carboxylic acid. Since the diketoacylindanes are themselves stable to acid and alkaline hydrolysis (Schwerin, *Ber.*, 1894, **27**, 104), their oxidation to simple acids apparently proceeds through the ester intermediates.

Oxidation of triacylmethane derivatives with hydrogen peroxide did not follow the same course as that of diketoacylindanes. Under neutral conditions tribenzoylmethane was unattacked, but on long standing dibenzoylacetylmethane decomposed slightly to unstable amorphous peroxides. In alkaline solution degradation to the corresponding simple carboxylic acids occurred. In acid conditions hydrolysis rather than oxidation took place.

Two mechanisms (Baeyer and Villiger, *Ber.*, 1899, **32**, 3625; Wacek and Eppinger, *Ber.*, 1940, **73**, 644) have been suggested for the oxidation of ketones to esters. The first, which involves the rearrangement of an intermediate peroxide, appears to be more satisfactory. It is supported by experiments on the oxidation of *cyclo*hexanone (Stoll and Scherrer, *Helv. Chim. Acta*, 1930, **13**, 142) and by the direct conversion of fluorenone mono-peroxide to the lactone of 2-hydroxydiphenyl-2′-carboxylic acid (Wittig and Pieper, *Ber.*, 1940, **73**, 295). Indirect evidence for the formation of an intermediate hydroxy-hydroperoxide (II) has been provided (Barnes and Lewis, *J. Amer. Chem. Soc.*, 1936, **58**, 947). The complete course of reaction between the diketoacylindanes and hydrogen peroxide may be represented in the following way :



Experimental.

Action of Hydrogen Peroxide.—(1) *On* 1 : 3-*diketo*-2-*acetylindane*. The triketone was prepared by Kilgore's, Ford, and Wolfe's modification (*loc. cit.*) of Schwerin's method (*Ber.*, 1894, **27**, 104). There was a small increase in yield when the sodium methoxide recommended was replaced by sodamide.

In alkaline solution. In a typical experiment the ketone (1·0 g.) was dissolved in a slight excess of 0·5N-sodium hydroxide, and after addition of excess of a solution of pure hydrogen peroxide (0·75 g. of 50% aqueous solution), it was left at 0° for 8 days. The reaction mixture yielded on acidification a precipitate of unchanged ketone (0·1 g.) and phthalic acid (0·75 g.), m. p. and mixed m. p. 203° (decomp.). Ether extraction gave a trace of phthalic acid and acetic acid (0·15 g.); *p*-phenylphenacyl ester, m. p. and mixed m. p. 115°.

In acid solution. 1 : 3-Diketo-2-acetylindane (1·0 g.), dissolved in sulphuric acid (10 c.c. of 80% solution), was treated at 0° with aqueous hydrogen peroxide (0·75 g. of 50% solution). After the initial reaction had subsided the mixture was left at room temperature for 24 hours, and then poured on ice. Phthalic and acetic acids were obtained in quantitative yield.

In neutral solution. The ketone was dissolved in the minimum of absolute ether, treated with excess of ethereal hydrogen peroxide [5 c.c. of 20% solution; prepared by concentrating a dried ethereal extract of freshly distilled and concentrated hydrogen peroxide (approximately 25%)], and left for 21 days at room temperature. The reaction mixture, on evaporation and treatment with water, yielded a light yellow solid, which was separated by extraction with chloroform into insoluble phthalic acid (0·02 g.) and a mixture of unchanged ketone (0·22 g.) and white leaflets (0·70 g.), m. p. 96°, which were separated by crystallisation from ethyl acetate–light petrol (b. p. 40—70°) [Found, for the leaflets: C, 64·5, 64·4; H, 4·1, 4·1; *M* (cryoscopic in benzene), 192. $C_{11}H_8O_4$ requires C, 64·7; H, 3·9%; *M*, 204]. In alcoholic solution this product, 1 : 3-*diketo*-2-*acetoxyindane* (III*a*), has no action on ferric chloride or acidified potassium iodide but gives a series of colour reactions. It dissolves very slightly in water to give a yellow solution, but gives colourless solutions in non-polar solvents. In 2N-sodium hydroxide it gives a yellow solution which rapidly changes to a deep ultramarine-blue. On acidification in the absence of oxygen this passes reversibly from blue (pH 11·0) through red (pH 6·0) to light yellow (pH 4·0). Both the red and the blue solution are rapidly decolorised through atmospheric oxidation. An alcoholic solution develops a strong purple stain on the human skin after several hours.

(2) *On* 1 : 3-*diketo*-2-*acetoxyindane*. The indane (0·10 g.), when dissolved in 2N-sodium hydroxide to give a blue solution or in the form of its yellow solution in 2N-sodium carbonate, reacted vigorously with excess of hydrogen peroxide. Acidification of the mixture gave phthalic acid in quantitative yield. Similarly in sulphuric acid solution (80%) quantitative oxidation to phthalic and acetic acids occurred.

Characterisation of 2-*hydroxy*-1 : 3-*diketoindane*. When air was blown through the acidified solution obtained on alkaline hydrolysis of 1 : 3-diketo-2-acetoxyindane (0·20 g.), a white solid (0·18 g.), m. p. 236° (decomp.), was precipitated. This was identified as hydrindantin hydrate (Ruhemann, *loc. cit.*) (Found: C, 60·5; H, 3·9. Calc. for $C_{18}H_{10}O_6,2H_2O$: C, 60·3; H, 3·9%) by m. p. and mixed m. p. The same product was formed on acidification of the alkaline hydrolysis solution of 1 : 3-diketo-2-acetoxyindane with an alcoholic solution of 1 : 2 : 3-triketoindane hydrate.

(3) *On* 1 : 3-*diketo*-2-*benzoylindane*. The indane (prepared after the manner of Schwerin, *loc. cit.*) in 2N-sodium hydroxide solution reacted with excess of hydrogen peroxide more slowly than did the acetyl derivative to give, together with a trace of unchanged ketone, phthalic and benzoic acids, which were separated and identified by mixed m. p. determination. In sulphuric acid quantitative yields of these acids were also obtained.

A solution of 1 : 3-diketo-2-benzoylindane (1·0 g.) in the minimum of absolute ether, on treatment with a large excess of ethereal hydrogen peroxide (7 g. of 20% solution) during 20 days, gave on evaporation a light yellow solid from which phthalic acid (0·1 g.), benzoic acid (0·05 g.), and a white solid (0·70 g.), m. p. 136·5—137°, were obtained. This solid crystallised as prisms from ethyl acetate–light petrol (b. p. 40—60°) [Found: C, 72·2; H, 3·9; *M* (cryoscopic in benzene), 258. $C_{16}H_{10}O_4$ requires C, 72·2; H, 3·8%; *M*, 266]. This product, 1 : 3-*diketo*-2-*benzoyloxyindane* (III*b*), gives similar colour reactions to the acetyl analogue. In 2N-sodium hydroxide the first-formed yellow solution changes more slowly than (III*a*) to deep ultramarine-blue. Alkaline hydrolysis of (III*b*) under hydrogen gave benzoic acid and 2-hydroxy-1 : 3-diketoindane, characterised, as previously, through conversion into hydrindantin.

(4) *On tribenzoylmethane*. Tribenzoylmethane (0·50 g.), prepared from dibenzoylmethane (*Org. Synth.*, Coll. Vol. I, 1941, 205) by the procedure of Birckenbach *et al.* (*Ber.*, 1932, **65**, 1071), was dissolved in 2N-sodium hydroxide solution and treated with excess of hydrogen peroxide (1·0 g. of 50% solution) overnight at room temperature. Concentration and acidification of the colourless solution yielded benzoic acid (0·47 g.), m. p. 122°. In sulphuric acid (10 c.c.) at 0°, hydrogen peroxide (1 c.c. of 50% solution) also converted the triketone (0·5 g.) into benzoic acid. Under neutral conditions (nitrobenzene solution or ethereal suspension) hydrogen peroxide had no action on the ketone over a period of 28 days.

(5) *On dibenzoylacetylmethane*. The methane (Claisen and Falk, *Annalen*, 1896, **291**, 25) in alkaline solution was degraded completely by hydrogen peroxide at room temperature in 3 days. Benzoic acid was isolated from the acidified solution in quantitative yield. In sulphuric acid solution (15 c.c.) at 0°, dibenzoylacetylmethane (0·5 g.) was hydrolysed to dibenzoylmethane (0·40 g.), m. p. and mixed m. p. 77°, in the absence of hydrogen peroxide.

Treatment of the keto-form of dibenzoylacetylmethane (1·0 g.) in ether with ethereal hydrogen peroxide (2 c.c. of 10% solution) at room temperature for 7 days yielded, besides unchanged material (0·3 g.), benzoic acid (0·2 g.) and a crude peroxide (m. p. 80—90°) which sublimed at 70—80°/0·01—0·02 mm. and readily liberated iodine from acidified potassium iodide. No pure material was isolated from the crude product.

The enolic form of dibenzoylacetylmethane (0·5 g.), m. p. 85° (107°; Claisen and Falk, *loc. cit.*), on

standing in ethereal hydrogen peroxide for 30 days, yielded unchanged product (0·45 g.) and a trace (0·02 g.) of an amorphous peroxide.

The analyses were by Messrs. C. L. Carter and J. A. Mills.

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14. *Addition of Dinitrogen Tetroxide to Olefins. Part IV. The Butylenes.*

By NORMAN LEVY, CHARLES W. SCAIFE, and A. E. WILDER-SMITH.

This paper deals mainly with the addition of dinitrogen tetroxide to *iso*butylene, and the application of the same procedure to the *n*-butylenes is described.

Normal addition to give dinitrobutanes and nitrobutyl nitrites requires an ether or ester solvent. The nitro-nitrites are partly oxidised to nitro-nitrates in the reaction, and the remainder are converted into nitrobutanols by water treatment at an early stage for safe and efficient separation of products. Total yields of pure products from *iso*butylene average 70—80%, made up of 35—42% of 1 : 2-*dinitro*isobutane, 25—30% of *nitro*-tert.-*butanol*, 2% of *nitro*-tert.-*butyl nitrate*, and 5—9% 1 : 3-*dinitro*-2-*methylpropan*-2-*ol*, the last three compounds being derived from nitro-*tert.*-butyl nitrite first formed. Addition of oxygen with the *iso*butylene sharply increases the proportion of the nitrate at the expense of the dinitro-paraffin. Only two modes of addition of dinitrogen tetroxide in ether type solvents were found: (i) as two nitro-groups, and (ii) as one nitro- and one nitrite group, the latter always being attached to the carbon atom with fewer hydrogen atoms. Addition of dinitrogen trioxide follows a similar rule in forming nitronitroso*iso*butane, the nitroso-group becoming attached to the tertiary carbon atom of *iso*butylene.

PART I (Levy and Scaife, *J.*, 1946, 1093) gave a general introduction to the series of papers on addition of dinitrogen tetroxide to olefins, while Parts II (Levy, Scaife, and Wilder-Smith, *J.*, 1946, 1096) and III (Levy and Scaife, *J.*, 1946, 1100) referred to the addition to ethylene and propylene respectively. The present paper extends the investigation to a study of the addition of dinitrogen tetroxide to the butylenes.

iso*Butylene.*

Previous work on the reaction between *iso*butylene and nitrogen oxides, including the tetroxide, is not extensive and has two outstanding deficiencies: (i) isolation and direct identification of products was incomplete; (ii) the rôle of reaction medium was insufficiently studied. The instability of the product, particularly when prepared from or in the presence of dinitrogen trioxide and the oxidising character of the tetroxide itself, present further difficulties. Sidorenko (*J. Russ. Phys. Chem. Soc.*, 1906, **38**, 955) treated *iso*butylene in ether with nitrous fumes (from arsenious oxide and nitric acid) obtaining *iso*butylene " nitrosite ", m. p. 80°, and a blue liquid. The solid gave a blue melt and could be reduced to the diamine. He also found that nitrogen tetroxide and *iso*butylene in ether gave a small amount of the bisnitrosate [dimeric $CMe_2(O{\cdot}NO_2){\cdot}CH_2{\cdot}NO$], m. p. 104°, and, as main product, a blue liquid which could be reduced in small yield to *iso*butylenediamine, but Strack and Fanselow (*Z. physiol. Chem.*, 1929, **180**, 153) failed to confirm this reduction. Ipatieff and Solonina (*J. Russ. Phys. Chem. Soc.*, 1901, **33**, 496) prepared the oxime $CMe_2(O{\cdot}NO_2){\cdot}CH{:}NOH$, m. p. 114—115°, from the reaction between *iso*butylene and amyl nitrite in acetic acid with the addition of nitric acid; the compound reacted with potassium cyanide to give 2-cyano*iso*butaldoxime, $CMe_2(CN){\cdot}CH{:}NOH$. More recently Michael and Carlson (*J. Org. Chem.*, 1940, **5**, 1) examined the reaction with nitrous fumes in both the gas and the liquid phase. The gas-phase reaction was accompanied by pronounced oxidation, and reaction in liquid dinitrogen tetroxide or light petroleum gave bis(*iso*butylene nitrosate) in varying small yields not exceeding 13%. The liquid product from reaction in ether was apparently more stable to distillation at low pressure but, other than a small amount of bis(nitronitroso*iso*butane), no pure products were isolated and therefore reduction was used as a means of identification. Both the crude mixture and the distilled portion gave *iso*butylamine assumed to have arisen from 1-nitro*iso*butylene, and di*iso*butylamine, supposed to have been formed together with *iso*butylamine from 1 : 2-dinitro*iso*butane. As in the work of Strack and Fanselow (*loc. cit.*) no *iso*butylenediamine was obtained, though it has now been obtained from 1 : 2-dinitro*iso*butane. Part of the distilled oil gave on reduction practically equimolar amounts of amino-*tert.*-butanol and ammonia, thought to have been formed from nitro-*tert.*-butyl nitrite. Michael and Carlson deduced from this that 1-nitro*iso*butylene constituted 5—12%, nitro-*tert.*-butyl nitrite 16—23%, and 1 : 2-dinitro*iso*butane at least 12% of the addition product.

The present investigation has shown that the course of reaction as in the case of propylene (Part III, *loc. cit.*) is profoundly affected by the solvent in that normal addition requires an ether or ester medium. Under appropriate conditions, oxidation reactions and nitronitroso*iso*butane formation can be suppressed. The primary products are 1 : 2-*dinitroisobutane* (I) and nitro-*tert.*-butyl nitrite (II), and part of the latter is oxidised to nitro-*tert.*-butyl nitrate (III) :

$$\underset{\text{(I.)}}{CMe_2(NO_2)\cdot CH_2\cdot NO_2} \xleftarrow{N_2O_4} CMe_2{:}CH_2 \xrightarrow{ONO\cdot NO_2} \underset{\text{(II.)}}{CMe_2(O\cdot NO)\cdot CH_2\cdot NO_2} \xrightarrow{H_2O} \underset{\text{(IV.)}}{CMe_2(OH)\cdot CH_2\cdot NO_2}$$

$$\text{Oxidn.} \downarrow$$

$$CMe_2(O\cdot NO_2)\cdot CH_2\cdot NO_2 \quad \text{(III.)}$$

The nitrite (II) is less stable than its lower homologues (*e.g.*, nitroethyl and nitropropyl nitrites can be prepared from the nitro-alcohol and nitrous acid, but nitro-*tert.*-butyl nitrite has not been formed in this manner), and it decomposes during distillation, forming some 1-nitro*iso*butylene. Isolation of pure substances by distillation of the crude product is very difficult, as well as hazardous. The decomposition of the nitrite and the induced decomposition of accompanying products makes difficult the assessment of substances originally present. The action of bases on the materials (*q.v.*) also affects inferences drawn from reduction experiments. Conversion of the unstable nitrite (II) into *nitro*-tert.-*butanol* (IV) by treatment with cold water, however, permits safe and efficient separation of pure products in total yield of 70—80% on the *iso*butylene consumed.

The yields summarised below are taken from examples in which ether was used as solvent. Two of the examples are described in detail later.

Product.	Yield without oxygen, %.	Yield with oxygen, %. $O_2/C_4H_8 = 0{\cdot}27$.	$O_2/C_4H_8 = 1{\cdot}09$.	$O_2/C_4H_8 = 3{\cdot}2$.
	(*a*)		(*b*)	
1 : 2-Dinitro*iso*butane	42·6 (45·9)	36·2	25·7 (31·8)	18·3
Nitro-*tert.*-butanol	27·8 (36·5)	26·5	28·7 (35·9)	26·7
Nitro-*tert.*-butyl nitrate	1·9 (2·3)	7·8	11·8 (14·6)	30·0
1 : 3-Dinitro-2-methylpropan-2-ol	6·1 (8·0)	4·5	3·8 (9·0)	3·0
Total	78·4 (92·7)	75·0	70·0 (91·3)	78·0

Additional figures, shown in parenthesis, are the yields in the reaction mixture before separation, and have been given to show how completely the reported products account for *iso*butylene concerned. The corrected values shown in parenthesis for (*a*) are based on experimentally determined losses in extraction and separation of a synthetic mixture of that composition. For (*b*) a different procedure for obtaining the corrected values was employed. For the nitro-alcohols extracted from the aqueous layer an experimentally determined extraction efficiency of 80% was used and no account was taken of losses occurring during this distillation, while for the other materials the values were based on losses during the distillation of the insoluble oil which is accompanied by some decomposition and is incomplete. For calculation it was assumed that the decomposition losses for (I) and (III) were in proportion to their actual yields, and the distillation residue was taken as 1 : 3-*dinitro*-2-*methylpropan*-2-*ol* (V), as this compound was isolated when the residue was carefully distilled.

With no oxygen the corrected total yield on tetroxide is 94% and the ether loss is about 3%. The product (I) was characterised by formation of *iso*butylenediamine on reduction and by formation of 1-nitro*iso*butylene on reaction with aqueous alkali, ammonia, and other bases, (III) by formation of 1-nitro*iso*butylene on reaction with aqueous alkali and by comparison with the nitrate ester prepared by nitration of nitro-*tert.*-butanol, (IV) by formation and de-acetylation of the acetate, giving 1-nitro*iso*butylene, and by hydrolytic fission to nitromethane and acetone, and (V) by hydrolytic fission to nitroacetone. Dehydration of (IV) by phosphoric oxide in benzene gives some 1-nitro*iso*butylene but largely the isomeric nitro-butylene, 3-*nitro*-2-*methyl*-1-*propylene* (VI).

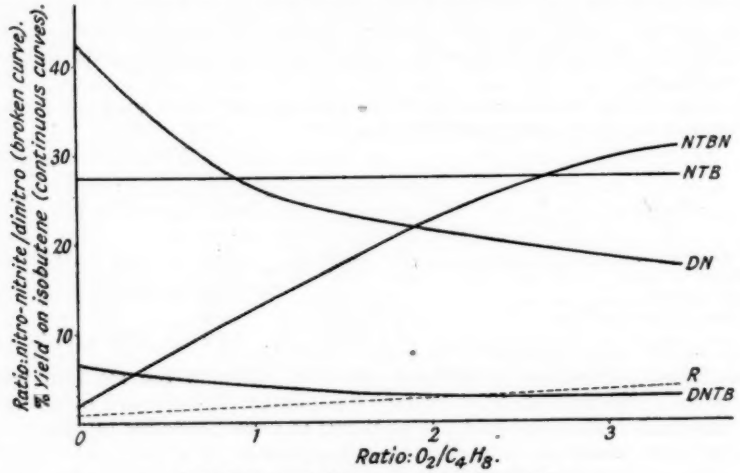
As (V) has been prepared by the addition of dinitrogen tetroxide and then water to (VI) it probably arises from (II) in the following manner :

$$\text{(II)} \xrightarrow{-HNO_2} \underset{\text{(VI.)}}{CH_3\cdot C(CH_2)\cdot CH_2\cdot NO_2} \xrightarrow{N_2O_4} CH_3\cdot C(CH_2\cdot NO_2)(ONO)\cdot CH_2\cdot NO_2 \xrightarrow{H_2O} \underset{\text{(V.)}}{CH_3\cdot C(CH_2\cdot NO_2)(OH)\cdot CH_2\cdot NO_2}$$

The table clearly shows that modes of addition other than as two nitro-groups or as one nitro- and one nitrite group do not occur to any substantial extent.

Discussion.—(a) *Effect of reaction medium* (cf. Parts I and III, *locc. cit.*). The reaction medium has been varied by the use of several classes of solvent, and by reaction in liquid dinitrogen tetroxide, in liquid *iso*butylene, and in the gas phase in a few experiments. In the gas phase, although it is possible to control the accompanying oxidation reaction even at 150° and to collect in good yield an oil which is fairly stable to distillation, dinitro*iso*butane has not been isolated, in contrast to the results with ethylene at 100°. Liquid media were more promising but the addition to give dinitro-formation only took place when ethers or esters were employed as solvents. Reaction in other solvents (*e.g.*, carbon tetrachloride, methylene chloride, light petroleum) or in the absence of a solvent gives rise to oxidation, and the main products isolated are the nitrate of α-hydroxy*iso*butyric acid (VII) and the nitrate of α-hydroxy*iso*-butaldoxime.

Oxidation reactions are largely suppressed and the desired reaction favoured by the following solvents: diethyl ether, di-*n*-propyl ether, dioxan, benzyl methyl ether, methylal, acetal, tetrahydropyran, tetrahydrofuran, ethyl acetate, and amyl acetate. There is some attack on the solvent in certain cases, and of the solvents mentioned the first three and the last two are the most suitable. These solvents are thought to moderate the oxidising tendency of N_2O_4



Variation of yield with O_2/C_4H_8 *ratio.*

DN = *Dinitro*isobutane. NTB = *Nitro*-tert.-*butanol*. NTBN = *Nitro*-tert.-*butyl nitrate*.
DNTB = *Dinitro*-tert.-*butanol*.
R = *Ratio of nitro-nitrite to dinitro-addition corrected for* 20% *extraction loss of nitro*-tert.-*butanol*.

through molecular complex formation between the N_2O_4 and the free electrons of the oxygen atom, and this view is supported by the actual separation of a labile solid complex, $C_4H_8O_2,N_2O_4$, from dioxan. With methyl 2-nitroethyl ether and 2 : 2′-dichlorodiethyl ether as solvents the nitrate of α-hydroxy*iso*butyric acid is produced, and, as with these ethers there is reduced electron-availability at the oxygen atom due to their electron-attracting substituents, it is apparent that the greater the electron availability the less the oxidising tendency of the dinitrogen tetroxide. Formic esters (ethyl and *iso*butyl formate), as would be expected on this theory, do not give as effective control of the oxidising tendency of N_2O_4 as do the acetates, and act as intermediate types giving rise both to dinitro*iso*butane, etc. (p. 58), and to the nitrate of α-hydroxy*iso*butyric acid.

Diethyl ether and dioxan have been examined in the greatest detail. The former is preferable because its low boiling point makes separation easier. Dioxan has given slightly higher yields of dinitro*iso*butane (45%), but gives the disadvantages of high boiling point and ready condensation of the solid complex in vapour lines.

(b) *Effect of oxygen.* The addition of oxygen during the reaction gives products more stable to distillation and prevents the formation of bis(nitronitroso*iso*butane) (VIII) which arises from any dinitrogen trioxide produced in the reaction (see p. 59). (VIII) is formed as one of the main products, together with dinitro*iso*butane and nitro-*tert.*-butanol when N_2O_3 reacts with *iso*butylene in ether.

With increasing partial pressure of oxygen in the inlet gas the yield of (III) rises and that of

(I) falls. As a result of the large change in composition of the product mixture, separation of dinitro*iso*butane by freezing becomes more difficult and fractional distillation becomes necessary. Yields of the four products with varying oxygen–*iso*butylene ratios are plotted in the figure. Taking nitro-*tert.*-butanol, nitro-*tert.*-butyl nitrate and 1 : 3-dinitro-2-methylpropan-2-ol as all derived from the nitro-nitrite, the ratio of $(^-NO_2)(^-ONO)$ addition to $(^-NO_2)(^-NO_2)$ addition has been calculated and plotted against the oxygen–*iso*butylene ratio in the figure, which shows a linear relationship between the two ratios. For this purpose the nitro-alcohol yields are corrected for 20% extraction loss but no correction is made for distillation losses.

The following approximate relation holds :

$$\frac{A_{(^-NO_2)(^-ONO)}}{A_{(^-NO_2)(^-NO_2)}} = 1 + \frac{P_{O_2}}{P_{C_4H_8}}$$

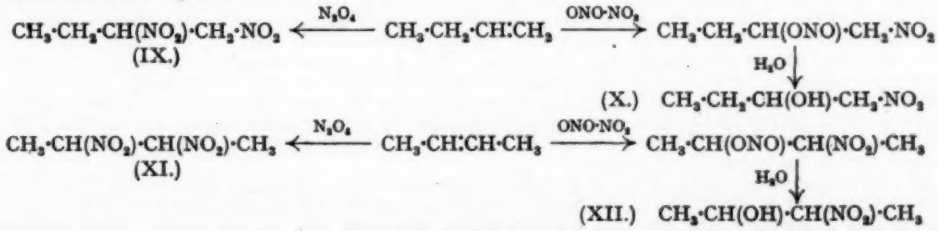
where $A_{(^-NO_2)(^-ONO)}$ = % C_4H_8 converted into nitro-nitrite,
$A_{(^-NO_2)(^-NO_2)}$ = % C_4H_8 converted into dinitro*iso*butane,
P_{O_2} and $P_{C_4H_8}$ = partial pressures of oxygen and *iso*butylene respectively.

Addition of oxygen thus influences the balance between nitro-nitrite and dinitro-compound in a regular manner.

It has been shown that the lower nitro-nitrites are readily oxidised to nitro-nitrates by dinitrogen tetroxide and oxygen in ether, and this suggests a means of formation of nitro-*tert.*-butyl nitrate. However, this does not explain the concurrent diminution of dinitro*iso*butane yield, and it seems probable that oxygen acts in a more direct fashion. Furthermore, the amount of *iso*butylene absorbed is not affected by the presence of oxygen, and mere dilution of the tetroxide does not show any marked influence on the proportions of products, so that concentration changes are not the deciding factor. Formation of olefin oxide, followed by tetroxide addition to give nitro-nitrate, does not seem likely since, apart from other considerations, attempts to form nitroethyl nitrate from ethylene oxide and tetroxide under similar conditions gave only water-soluble oxidation products. The suggestion is therefore made that dissolved oxygen gives rise to $\overset{+}{N}O_2$–ONO_2 assemblies, either immediately or in the course of addition, leading to nitro-nitrate formation in place of dinitro*iso*butane. One further result related to this observation is that if the reaction is carried out by passing nitric oxide and a large excess of oxygen into a 10% solution of *iso*butylene in ether at −10°, the products isolated by the usual separation procedure are mainly nitro-*tert.*-butanol and nitro-*tert.*-butyl nitrate, with only 5% yield of dinitro*iso*butane.

Normal Butylenes.

The same procedure has been applied to 1- and 2-butylenes with formation of the dinitrobutanes and the nitrobutanols as expected. Thus, 1-butylene gives 1 : 2-*dinitrobutane* (IX) and 1-nitrobutan-2-ol (X), while 2 : 3-dinitrobutane (XI) and 2-nitrobutan-3-ol (XII) are obtained from 2-butylene.



Demjanov (*Ber.*, 1907, **40**, 245) previously investigated the reaction between 1-butylene and nitrous fumes (from arsenious oxide and nitric acid), obtaining butylene " nitrosite ", and he also isolated a similar compound from the reaction between 2-butylene and dinitrogen pentoxide (*Ann. Inst. Agron. Moscow*, 1894, **4**, 155). A 2 : 3-dinitrobutane has been reported as a solid, m. p. 41°, from the spontaneous decomposition of the silver salt of nitroethane (Angeli and Allessandri, *Atti R. Accad. Lincei*, 1886, **19**, 784). Both nitro-alcohols have been prepared before, 2-nitrobutan-3-ol from nitroethane and acetaldehyde (*e.g.*, Henry, *Ber.*, 1900, **33**, 3169) and 1-nitrobutan-2-ol from nitromethane and propaldehyde (*e.g.*, Jones and Kenner, *J.*, 1930, 919).

Yields are as follows : (*a*) from 1-butylene, 33% of 1-nitrobutan-2-ol and 39·3% of insoluble

oil (largely 1 : 2-dinitrobutane); (*b*) from 2-butylene, 34·5% of 2-nitrobutan-3-ol and 30% of insoluble oil (largely 2 : 3-dinitrobutane). The nitrobutanol obtained from 1-butylene is derived from the expected nitro-nitrite, that is, with the nitrite group attached to the carbon with fewer hydrogen atoms. The amounts of nitrobutyl nitrate formed are quite small, oxygen not being used in the reaction. Characterisation of the products is detailed on p. 60: (IX) by formation of 1 : 2-diaminobutane on reduction and by formation of propaldehyde on reaction with aqueous alkali accompanied with oxidation hydrolysis, (X) by formation and de-acetylation of the acetate giving 1-nitro-1-butylene, (XI) by formation of 2 : 3-diaminobutane on reduction and by formation of acetaldehyde on reaction with aqueous alkali accompanied by hydrolysis, (XII) by formation and de-acetylation of the acetate giving 2-*nitro*-2-*butylene*. The nitro-alcohols (X) and (XII) were also characterised by hydrolysis to the aldehydes in a similar way to the dinitro-compounds.

Experimental.

Reagents.—Pure liquid dinitrogen tetroxide and dry ether were prepared as previously described (Part II, *loc. cit.*). *iso*Butylene of high purity was prepared by dehydration of *tert.*-butanol over active alumina, and the normal butylenes by dehydration of *iso*butanol followed by fractional distillation. Nitric oxide was prepared by addition of concentrated sulphuric acid to a well-stirred paste of sodium nitrite and water, and was dried by passage through concentrated sulphuric acid and over calcium chloride. Dinitrogen trioxide was prepared by passing nitric oxide through pure liquid dinitrogen tetroxide at −10° until no more was absorbed, and purified by distillation in a rapid stream of nitric oxide. The vapours were passed through a trap to collect any trace of nitric acid and then through a cooling coil at −20° where the trioxide collected as a blue liquid in a cooled receiver. Moisture was excluded from the apparatus by calcium chloride tubes.

iso*Butylene.*

Diethyl Ether as Solvent. Dinitrogen Tetroxide Addition.—The reaction procedure is similar to that described for propylene (Part III, *loc. cit.*), but because of the higher boiling point of *iso*butylene the liquid tetroxide may be slowly added to a stirred 10% solution of *iso*butylene in ether at −10°. *iso*Butylene reacts somewhat more rapidly than propylene. Oxides of carbon in the exit vapours correspond to less than 0·1% on the *iso*butylene. In the absence of oxygen, interference by nitrogen trioxide addition is prevented by absorbing no more than 0·8 mol. of *iso*butylene per mol. of tetroxide and by not exceeding tetroxide concentrations of 40% by weight in ether for batch reactions. Circumstances which may give high general or local ratios of *iso*butylene to tetroxide should be avoided; *e.g.*, temperatures below −10° when gaseous *iso*butylene is passed into dissolved tetroxide, or high concentrations of *iso*butylene in ether when tetroxide is added dropwise. Prevention of the formation of nitronitroso-*iso*butane (VIII) is advisable since even in small quantities it interferes with the crystallisation of pure 1 : 2-dinitro*iso*butane. Oxygen, when used, is mixed with the *iso*butylene before absorption.

The separation procedure is similar to that described previously (Parts I and III, *locc. cit.*). *Nitro*-tert.-*butanol* is recovered from the aqueous extract together with a subsidiary fraction of 1 : 3-*dinitro*-2-*methylpropan*-2-*ol* and small amounts of 1 : 2-*dinitro*iso*butane* and nitro-*tert.*-butyl nitrate. Neutralisation of the aqueous layer with chalk before ether extraction gives pure nitro-*tert.*-butanol on first distillation and simplifies separation from the dinitro-alcohol. The separation of 1 : 2-dinitro*iso*butane obtained on cooling a methyl alcohol solution of the water-insoluble oil is not complete owing to the presence of other components, and, for full recovery, fractional distillation of the oil obtained from the filtrate is necessary. Considerable care is required, and the distillation flask must be cooled with a methyl alcohol solution containing solid carbon dioxide whenever gas evolution is marked. When oxygen is used, even in small amount, for the reaction much of the dinitro*iso*butane remains in solution on cooling because of the increased content of nitro-*tert.*-butyl nitrate, and a somewhat laborious fractional distillation is then the only satisfactory means of separation. The oil, however, is much more stable than that obtained in the absence of oxygen. With no oxygen the main loss occurs in the recovery of nitro-*tert.*-butanol, which is about 75% efficient mainly owing to incomplete extraction and hydrolytic fission of the nitro-alcohol. With oxygen, besides the loss of nitro-*tert.*-butanol there is also appreciable loss of product in the distillation of the water-insoluble oil due to some decomposition and unstable distillation residue. The following are accounts of typical experiments showing the procedure in the absence, and in the presence, of oxygen.

(*a*) Dry *iso*butylene (270 g. or 107 l. at N.T.P.) was passed into a solution of tetroxide (750 g.) in dry diethyl ether (1750 g.) at 0° during 3½ hours. Ether and excess of tetroxide were removed in the continuous film evaporator, the reaction product falling dropwise into 1 l. of water. Recovered ether weighed 1690 g. (97% of original weight) and recovered tetroxide 300 g. After the oil–water mixture had been stirred, the oil was separated and further washed with successive quantities of 800 c.c., 400 c.c., and 400 c.c. of water, leaving 431 g. of insoluble oil. The bulked aqueous layers were continuously extracted with ether for 48 hours, the extract dried (Na_2SO_4), the ether removed under reduced pressure, and the residue distilled to give the following fractions: (i) 8·25 g., b. p. 42—50°/1 mm.; (ii) 138·9 g., b. p. 50—70°/1 mm.; (iii) 17·3 g., b. p. 70—106°/1 mm.; (iv) 33·5 g., b. p. 106—120°/1 mm. The first three fractions were mixed and redistilled to give 147·8 g. of nitro-*tert.*-butanol, b. p. 56°/<1 mm. (Found: C, 40·0; H, 7·4; N, 11·7. $C_4H_9O_3N$ requires C, 40·3; H, 7·6; N, 11·8%), and 14·9 g., b. p. 69—70°/<1 mm., shown by estimation as in (*b*) to contain 6·0 g. of nitro-*tert.*-butyl nitrate and 8·9 g. of 1 : 2-dinitro*iso*butane. Fraction (iv) was crystallised from ether to give 1 : 3-dinitro-2-methylpropan-2-ol (Found C, 29·5; H, 4·8; N, 16·9. $C_4H_8O_5N_2$ requires C, 29·2; H, 4·9; N, 17·1%).

The 431 g. of insoluble oil were dissolved in 700 ml. of methyl alcohol and cooled with stirring in a jacket at −70° to give 261 g. of solid 1 : 2-dinitro*iso*butane (Found: C, 32·3; H, 5·6; N, 18·5. $C_4H_8O_4N_2$

requires C, 32·4; H, 5·4; N, 18·9%). After removal of the methyl alcohol from the filtrate, the oil was dried by azeotropic distillation with 180 ml. of benzene, giving 132·2 g. of dry oil. Fractional distillation, with occasional cooling of the boiler to check decomposition, gave the following fractions: (i) 14·3 g., b. p. 30—60°/1—2 mm.; (ii) 44·7 g., b. p. 60—90°/1—2 mm.; (iii) 13·6 g., b. p. 90—134°/1—2 mm.; residue, 25·5 g.; distillation loss as gaseous decomposition products and volatile material containing some 1-nitro*iso*butylene, 34·1 g. Freezing fraction (ii) in methanol at −70° gave a further 24·6 g. of 1 : 2-dinitro*iso*butane and a residual oil which, after admixture with fractions (i) and (iii) was redistilled to give 11·4 g. of nitro-*tert.*-butanol, 9·4 g. of nitro-*tert.*-butyl nitrate, 9·0 g. of dinitro*iso*butane, and 16·4 g. of 1 : 3-dinitro-2-methylpropan-2-ol. The total quantities of the four compounds and the yields on *iso*butylene were 303·5 g. of dinitro*iso*butane (42·6%), 159·2 g. of nitro-*tert.*-butanol (27·8%), 15·4 g. of nitro-*tert.*-butyl nitrate (1·9%), and 49·9 g. of 1 : 3-dinitro-2-methylpropan-2-ol (6·1%).

(*b*) The quantities used were *iso*butylene 127 g. (53·5 l.), oxygen 58·7 l., dinitrogen tetroxide 301 g., dry diethyl ether 700 g., requiring 1 hour's absorption time at 0°. Removal of ether and excess of tetroxide followed by treatment of the product with 500 c.c. and 400 c.c. portions of water gave 177 g. of insoluble oil. Neutralisation of the aqueous layers followed by extraction and distillation gave two sharp fractions: (i) 77·4 g., b. p. 50—56°/<1 mm.; (ii) 14·1 g., b. p. 108—111°/<1 mm.; (iii) 0·9 g., intermediate fraction; residue, 1·8 g. Fraction (i) solidified in the receiver and was pure nitro-*tert.*-butanol. Fraction (ii) was practically pure 1 : 3-dinitro-2-methylpropan-2-ol.

The insoluble oil gave only a little dinitro*iso*butane on freezing in methanol at −70° and was therefore distilled under reduced pressure without difficulty and with a residue of 16·1 g. Redistillation gave two fractions: (i) 77·4 g., b. p. 74—77°/<1 mm.; (ii) 52·8 g., b. p. 80—82°/1 mm. Fraction (ii) solidified in the receiver and was pure 1 : 2-dinitro*iso*butane. Fraction (i) was a mixture of dinitro*iso*butane and nitro-*tert.*-butyl nitrate which was analysed by reaction with aqueous alkali, removal of 1-nitro*iso*butylene with benzene, and determination of total nitrogen and nitrite nitrogen in the aqueous layer. Two such analyses in agreement gave 43·4% of dinitro*iso*butane and 56·6% of nitro-nitrate. Thus, total amounts and yields on *iso*butylene were 86·4 g. of dinitro*iso*butane (25·7%), 43·8 g. of nitro-*tert.*-butyl nitrate (11·8%), 77·4 g. of nitro-*tert.*-butanol (28·7%), and 14·1 g. 1 : 3-dinitro-2-methylpropan-2-ol (3·8%).

(*c*) Dry nitric oxide and a large excess of oxygen were passed into a solution of *iso*butylene (29 g.) in ether (326 g.) at −5°. Removal of ether and excess of tetroxide followed by treatment of the product with water (200 c.c.) gave 44·6 g. of insoluble oil. Distillation of this oil, after drying by distillation with benzene, gave 41·0 g., b. p. 74—78°/<1 mm., which was analysed as before and shown to contain 39·7 g. of nitro-*tert.*-butyl nitrate (46·7% yield) and 1·3 g. of dinitro*iso*butane (1·7% yield). The aqueous layer yielded 12·6 g. of nitro-*tert.*-butanol (20·2% yield) and a residue containing 1 : 3-dinitro-2-methylpropan-2-ol.

Properties and Characterisation of Products—1 : 2-*Dinitroisobutane* (I). This is a white crystalline solid, m. p. 52—53° after recrystallisation from methyl alcohol. It distils in a vacuum to give a colourless liquid, b. p. 92°/*ca.* 1 mm., which readily solidifies on cooling. Although it is an explosive of moderate power (51·1% blasting gelatin in the mortar test), it is very insensitive to friction and impact, stable to storage at room temperature and at 50°, and withstands heating in vacuum at 100° for more than 40 hours.

iso*Butylenediamine*. (I) was reduced in glacial acetic acid with hydrogen at 80—100 atm. and Adams's platinum catalyst. As with the lower dinitro-paraffins dilute solutions were necessary and, hence, 0·5 g. of dinitro*iso*butane in 300 c.c. of glacial acetic acid was reduced at 80 atm. in the presence of 0·0234 g. of catalyst to give, after saturation with hydrogen chloride and evaporation of the acetic acid, 0·525 g. of crude hydrochloride (96%). This was dissolved in the minimum amount of alcohol, and 0·320 g. of pure iso*butylenediamine dihydrochloride* precipitated with ether (59% yield). After recrystallisation it melted at 302° (Found: Cl, 43·7; N, 17·8. $C_4H_{12}N_2,2HCl$ requires Cl, 44·1; N, 17·4%).

1-*Nitroisobutylene from* 1 : 2-*dinitroisobutane*. A solution of sodium hydroxide (81 g.) in water (300 c.c.) was added during ½ hour to a stirred suspension of dinitro*iso*butane (300 g.) in water (450 c.c.). The nitro-olefin separated as an oil, and together with a small amount extracted with ether from the aqueous layer was dried (Na_2SO_4) and distilled under reduced pressure to give 180 g. (88% yield) of nitro*iso*butylene, b. p. 56°/11 mm., $d_4^{20°}$ 1·048, $n_D^{20°}$ 1·468 (Found: C, 47·4; H, 6·9; N, 12·9. Calc. for $C_4H_7O_2N$: C, 47·5; H, 6·9; N, 13·9%).

Nitro-tert.-*butyl nitrate* (III). This was isolated on careful fractional distillation of fraction (i) of the insoluble oil (*b*) (Found: C, 29·5; H, 5·1; N, 17·3. Calc. for $C_4H_8O_5N_2$: C, 29·3; H, 4·9; N, 17·1%). The nitrate crystallises at about 6° and distils in a vacuum to give a colourless liquid, b. p. 78°/*ca.* 1 mm., $d_4^{20°}$ 1·283; $n_D^{20°}$ 1·449. The same nitrate is obtained by nitration of nitro-*tert.*-butanol. The nitration gives much better yields if nitrogen tetroxide is used in place of the usual nitric acid–sulphuric acid mixture. A slow stream of oxygen was passed through a mixture of nitro-*tert.*-butanol (130 g.) and dinitrogen tetroxide (950 g.) for 60 hours. The excess of nitrogen tetroxide was removed in a stream of oxygen, and the product (214 g.) stirred with 660 c.c. of water. The residue (93 g.) on distillation gave 2·7 g., b. p. <74°/*ca.* 1 mm., and 80·4 g. of nitro-*tert.*-butyl nitrate, b. p. 78—80°/*ca.* 1 mm. (Found: C, 29·4; H, 4·9; N, 17·1%). From the aqueous layer 50·5 g. of nitro-*tert.*-butanol were recovered. (Yield of nitrate on nitro-*tert.*-butanol converted, 73·4%.)

1-*Nitroisobutylene from nitro*-tert.-*butyl nitrate*. The method was the same as that used for 1 : 2-dinitro*iso*butane, except that stirring was continued for 3 hours and the solution made just acid before ether extraction. Quantities used were nitro-*tert.*-butyl nitrate (50 g.) in water (500 c.c.) and sodium hydroxide (12·5 g.) in water (500 c.c.); 25·7 g. (yield 83·5%) of 1-nitro*iso*butylene, b. p. 65°/14 mm., were obtained (Found: C, 47·5; H, 6·9; N, 14·2%).

Nitro-tert.-*butanol* (IV). This crystallises in needles, m. p. 26°. It distils under vacuum to give a colourless liquid, b. p. 66°/*ca.* 1. mm., $d_4^{20°}$ 1·132, $n_D^{20°}$ 1·443, and is somewhat hygroscopic.

Formation and de-acetylation of nitro-tert.-*butyl acetate*. *Nitro*-tert.-*butyl acetate* is prepared in almost theoretical yield by adding acetyl chloride to nitro-*tert.*-butanol in the cold and distilling the product under reduced pressure (Found: C, 44·4; H, 7·0; N, 8·9. $C_6H_{11}O_4N$ requires C, 44·7; H, 6·8; N, 8·7%). It has b. p. 60°/<1 mm., $d_4^{20°}$ 1·123, $n_D^{20°}$ 1·432. The acetate (30 g.) was heated with 2% potassium

carbonate for 1 hour at 65° and then distilled at 14 mm. The distillate was added to 1·5 vols. of ether, washed with water to remove acetic acid, dried, and distilled. This gave 14·8 g. (78% yield) of nitro-olefin (Found: C, 47·4; H, 6·9; N, 13·8%). Careful fractionation showed it to contain 1·05 g. of *3-nitro-2-methyl-1-propylene* (VI), b. p. 40—43°/13 mm., while the remainder was 1-nitro*iso*butylene, b. p. 56°/11 mm. Unlike the α-nitro-olefins, 3-nitro-2-methyl-1-propylene is not lachrymatory.

Hydrolytic fission of nitro-tert.*-butanol to nitromethane and acetone.* Nitro-*tert.*-butanol (40·5 g.) was heated with 1000 c.c. of distilled water in a stainless steel autoclave at 130—150° for 2 hours. The product was cooled and drained off and the autoclave washed with distilled water. The product was combined with the washings and fractionally distilled through a vacuum-jacketed silvered column (6 in. × 1 in. diameter, packed with 1/16 in. × 1/16 in. stainless steel gauze rings), using a reflux ratio of approximately 30 : 1. Acetone (12·96 g.) was collected, b. p. 56—58°, followed by a small intermediate fraction (2·1 g.), b. p. 58—62°, the nitromethane–water azeotrope, b. p. 82°, and a small aqueous fraction boiling up to 100°. The acetone fraction was pure (yield 66%). The nitromethane–water fraction contained 22 g. of water and 17·8 g. of nitromethane (yield 85·7%).

Dehydration of nitro-tert.*-butanol by phosphoric oxide.* Nitro-*tert.*-butanol (70 g.) and phosphoric oxide (120 g.) in benzene (500 c.c.) were heated on the water-bath for 40 minutes. The pale brown supernatant liquid was decanted, and the residual phosphoric oxide washed with 50 c.c. of hot benzene and the latter added to the benzene already decanted. The benzene was recovered through a column and the residue was distilled under reduced pressure through an efficient column to give (i) 22·8 g. (41·0%) of 3-nitro-2-methyl-1-propylene, b. p. 40—43°/13 mm. (Found: C, 47·4; H, 6·9; N, 14·2. $C_4H_7O_2N$ requires C, 47·5; H, 6·9; N, 13·9%), (ii) 12·1 g. (21·7%) of 1-nitro*iso*butylene, b. p. 57—60°/13 mm. (Found: C, 47·2; H, 6·9; N, 14·2%), and (iii) 4·45 g. of unchanged nitro-*tert.*-butanol.

1 : 3-*Dinitro-2-methylpropan-2-ol* (V). This is a white crystalline solid, m. p. 31°; it distils in a vacuum to give a colourless liquid, b. p. 108°/<1 mm., which is very difficult to crystallise.

Hydrolytic fission of (V) *to nitroacetone.* (V) (10 g.) was added slowly to stirred aqueous alkali (30·6 c.c. of 4·25N-sodium hydroxide) at room temperature, and after 1 hour the mixture was slowly acidified at 0° with 7·8N-hydrochloric acid; some white solid then separated. The aqueous solution was continuously extracted with ether, and the ether removed, leaving an oil which crystallised on cooling. Recrystallisation at −70° from ether gave 4·32 g. (69%) of nitroacetone, m. p. 51° (Found: C, 34·4; H, 5·2; N, 13·5. Calc. for $C_3H_5O_3N$: C, 35·0; H, 4·9; N, 13·6%). The nitroacetone was also identified by mixed melting point with material made from 2-nitro*iso*propanol (Part III, *loc. cit.*), and by preparation of the anil.

Synthesis of (V) *from 3-nitro-2-methyl-1-propylene.* The nitro-olefin (30 g.) in diethyl ether (300 c.c.) was added dropwise during 1 hour to dinitrogen tetroxide (30 g.) in ether (200 c.c.) at −10° and allowed to stand for 2 hours. The solvent was removed under reduced pressure, and the residual oil added to a little water. The aqueous mixture was extracted with ether and the extract distilled to give 22·1 g. of oil, b. p. 130—145°/2 mm., with gas evolution and a large residue. Redistillation gave 1 : 3-dinitro-2-methylpropan-2-ol, b. p. 106—108°/1 mm. (Found: C, 29·3; H, 5·0; N, 17·0%).

Miscellaneous Solvents. Dinitrogen Tetroxide Reaction.—(a) *Ethers and esters.* With dioxan, di-*n*-propyl ether, benzyl methyl ether, methylal, acetal, tetrahydropyran, ethyl acetate, and amyl acetate, using the same reaction and separation procedure as described under diethyl ether, (I), (III), (IV), and (V) were again obtained. Their yields were (1) for dioxan, of the same order as for diethyl ether as solvent, total 69%, (2) for ethyl acetate and amyl acetate, total 60%, that for (IV) being only about 10%, (3) for acetal, total about 50%, that for (IV) being 21%, (4) for the other solvents, total less than 50%, but only small-scale experiments were carried out. With the acetates and acetal, only small amounts of 1 : 2-dinitro*iso*butane (I) could be obtained on freezing, and distillation of the insoluble oil was necessary.

(I), (III), (IV), and (V) were not obtained on applying the same reaction and separation procedure with methyl 2-nitroethyl ether and 2 : 2′-dichlorodiethyl ether as solvents. The nitrate of α-hydroxy-*iso*butyric acid (VII) was formed, and was isolated in small yield by the procedure outlined in the account of the following experiment. *iso*Butylene (18 g.) was passed into a solution of tetroxide (61 g.) in dichlorodiethyl ether (150 g.) at −5°. The solvent and excess of tetroxide were removed under suction leaving 49·8 g. of oil, which was washed with 100 c.c. of water; a little oil (7·3 g.) then dissolved. The insoluble oil was distilled and gave the following fractions: (i) 18·25 g., b. p. <60°/1 mm., (ii) 0·3 g., b. p. 62—100°/1·5 mm.. (iii) 10·6 g., b. p. 100—110°/1·5 mm., and 6·3 g. residue. Fraction (iii) solidified in the receiver and after recrystallisation from light petroleum had m. p. 77° (Found: C, 31·7; H, 4·4; N, 9·5. Calc. for $C_4H_7O_5N$: C, 32·2; H, 4·7; N, 9·4%); cf. Duval (*Bull. Soc. chim.*, 1904, **31**, 246) who obtained the nitrate of α-hydroxy*iso*butyric acid as a solid, m. p. 78°, by the action of mixed nitric and sulphuric acids on the zinc salt of α-hydroxy*iso*butyric acid. The aqueous washings, after extraction with ether and distillation, gave a further 4 g. of (VII), making a total yield of 30·5%.

Using formic esters as solvents, (I), (III), (IV), (V), and (VII) were obtained. An account of an experiment using ethyl formate as solvent is given. *iso*Butylene (23 g.) was passed into a solution of tetroxide (57 g.) in ethyl formate (138 g.) at 0°. The solvent and excess of tetroxide were removed under suction leaving 50·0 g. of oil, which was washed with 700 c.c. and 250 c.c. of water, and left 27 g. undissolved. The aqueous washings were extracted with ether and the extract distilled to give 9·8 g., b. p. 50—139°/0·5—2·0 mm., and 3·5 g. of residue. Fractionation of the distillate gave 5·3 g. of nitro-*tert.*-butanol and 0·9 g. of the nitrate of α-hydroxy*iso*butyric acid. The insoluble oil was added to methyl alcohol (40 c.c.) and cooled to −70°; only a little dinitro*iso*butane separated. The oil was therefore distilled, and the distillate on redistillation gave the following fractions: (i) 1·3 g., b. p. 34—40°/<1 mm., (ii) 5·9 g., b. p. 65—94°/1 mm., (iii) 3·1 g., b. p. 94—108°/1 mm., (iv) 4·4 g., b. p. 108—114°/<1 mm. Fraction (ii) was added to methyl alcohol and cooled to −70°; dinitro*iso*butane was thus obtained, m. p. 52—53°. Fractions (iii) and (iv) were dissolved in benzene, light petroleum (b. p. 60—80°) added, and the mixture cooled; then the nitrate of α-hydroxy*iso*butyric acid separated, m. p. 75°. All products were characterised by analysis, mixed m. p. if solid, and reactions.

(b) *Liquid dinitrogen tetroxide.* Passage of *iso*butylene into cold dinitrogen tetroxide, followed by removal of excess of the latter, gave a yellow oil which on cooling to −70° deposited the nitrate of α-hydroxy*iso*butyric acid in 22% yield. The residual oil, from which no (I), (III), (IV), or (V) could be separated, represented about 40% of the *iso*butylene.

(c) *Liquid* iso*butylene.* Passage of gaseous tetroxide into liquid *iso*butylene at −10°, followed by removal of excess of *iso*butylene, gave a green oil in good yield which deposited a small amount of the nitrate of α-hydroxy*iso*butaldoxime, m. p. 110° (Found: C, 31·8; H, 5·1; N, 19·3. Calc. for $C_4H_8O_4N_2$: C, 32·4; H, 5·4; N, 18·9%) (Ipatieff and Solonina, *loc. cit.*, give m. p. 114—115°). From the remaining oil no (I), (III), (IV), or (V) could be separated.

(d) *Carbon tetrachloride.* Rapid absorption took place when *iso*butylene (56 g.) was passed into a cooled solution of tetroxide (100 g.) in carbon tetrachloride (300 g.). Sufficient oxidation occurred to form a small separate layer of aqueous nitric acid. The solvent was removed under reduced pressure and the oil mixed with an equal volume of methyl alcohol and cooled; a little of the nitrate of α-hydroxy-*iso*butaldoxime then separated. The remaining oil was washed three times with 2 vols. of water and a 5% yield of (VII) isolated from the aqueous extract. Subsequent distillation of the washed oil caused decomposition with the formation of 4 g. of 1-nitro*iso*butylene. No (I), (III), (IV), or (V) could be separated.

(e) *Methylene chloride.* Rapid absorption took place when *iso*butylene (75 g.) was passed into a cooled solution of tetroxide (120 g.) in methylene chloride (270 g.). Two phases separated as with carbon tetrachloride. The solvent was removed under reduced pressure and a methyl alcohol solution of the oil cooled; a little (VII) but no (I) then separated. The residual oil was unstable to distillation. No (I), (III), (IV), or (V) could be separated using the procedure described under diethyl ether as solvent.

(f) *Light petroleum* (*b. p.* 60—80°). *iso*Butylene (103 g.) was passed into a solution of tetroxide (240 g.) in petroleum (722 g.) at 0°. Two layers were formed. The solvent and excess of tetroxide were removed under reduced pressure, and the oil washed with 600 c.c., 250 c.c., and 250 c.c. of water. The aqueous extract yielded 22·6 g. of distillate, b. p. <91°/2 mm., which fractionation and analysis showed contained mainly non-nitrogenous compounds, although a small amount of nitro-*tert.*-butanol was isolated. No deposit was obtained on cooling a methyl alcohol solution of the insoluble oil, nor was any pure product obtained on distillation.

Diethyl Ether as Solvent. Dinitrogen Trioxide Addition.—*iso*Butylene (29 g.) and ether (216 g.) were stirred to −5° in a flask (fitted with a reflux condenser through which methyl alcohol, cooled to −70°, circulated) and a solution of dinitrogen trioxide (43 g.) in ether (110 g.) added over 1½ hours. The trioxide solution was freshly prepared and was stored at −70° before use. The ether solution turned bright blue, and crystals separated. The solvent was removed under reduced pressure and the residue stirred with 200 c.c. of water and left for 48 hours. On filtration, a solid (16·6 g.) was obtained, which gave white crystals on crystallisation from alcohol, m. p. 81°, giving a blue melt (Found: C, 36·3; H, 6·2; N, 21·2. Calc. for $C_4H_8O_3N_2$: C, 36·3; H, 6·1; N, 21·2%.) The aqueous layer was separated, extracted with ether for 48 hours, and the ether extract distilled to give 8·9 g. of nitro-*tert.*-butanol and 3·0 g. of 1 : 3-dinitro-2-methylpropan-2-ol. The insoluble oil (21 g., after drying by azeotropic distillation with benzene) gave only a little dinitro*iso*butane (I) on cooling a methyl alcohol solution, and therefore the content of (I) was estimated by interaction of the oil (10 g.) with aqueous alkali when (I) gave 1-nitro*iso*butylene (3·3 g.).

The solid, m. p. 81°, was characterised as bis-(1-nitro-2-nitroso*iso*butane) (VIII) (cf. Sidorenko, *loc. cit.*) by (*a*) reaction with acetic anhydride in the presence of concentrated sulphuric acid to give nitro-*tert.*-butyl acetate which was de-acetylated as before to 1-nitro*iso*butylene, and (*b*) reaction with alcoholic potash or aniline to give 1-nitro*iso*butylene. Details are given below.

*Conversion of Bis(nitronitroso*iso*butane) into Nitro*iso*butylene.*—(a) via *Nitro*-tert.*-butyl acetate.* The nitroso-compound (10 g.) was added slowly to 20 c.c. of acetic anhydride (20 c.c.) and concentrated sulphuric acid (4 drops), the temperature being maintained at 40—45°. A further 15 c.c. of anhydride and a few drops of acid were added to complete the reaction. Excess of anhydride was removed under reduced pressure, the residue dissolved in benzene and washed with water, dried, and then distilled to give 4·2 g. of nitro-*tert.*-butyl acetate, b. p. 44°/<1 mm., which when de-acetylated as before gave 2·0 g. of 1-nitro*iso*butylene, b. p. 56—58°/12 mm., yield 26%.

(b) *By reaction with alcoholic potash.* The nitroso-compound (5·0 g.) was added with stirring to 10% alcoholic potash (36 c.c.), followed by water (50 c.c.), and acidification with concentrated hydrochloric acid at 0°. The solution was extracted with ether to give 1·6 g. of nitro*iso*butylene, yield 42%.

(c) *By reaction with aniline.* The nitroso-compound (4·0 g.) was added to a boiling solution of aniline (2·8 g.) in alcohol (10 c.c.) under reflux, the solution turning olive-green and then pale yellow. After 2 hours, the alcohol was removed and the residue distilled under reduced pressure to give 1·9 g. of nitro*iso*butylene, yield 62%.

Normal Butylenes.

Diethyl Ether as Solvent. Dinitrogen Tetroxide Addition.—The procedures for reaction, removal of solvent and excess of tetroxide, treatment of crude oil with water, and extraction of nitro-alcohol from the aqueous layer are all identical with those used for *iso*butylene. On the other hand, the insoluble oil from 1-butylene deposits no solid when cooled in methyl alcohol solution and gives liquid 1 : 2-*dinitrobutane* on distillation. In the case of 2-butylene, only a small amount of a solid form of 2 : 3-dinitrobutane comes out on cooling, and distillation gives a liquid form, from which some more of the solid can be obtained by freezing. The amounts of nitrobutyl nitrate formed in both cases are quite small, oxygen not being used in the reaction. The following are accounts of typical experiments.

1-*Butylene.* The quantities used were 45·8 g. (18·9 l.) of 1-butylene, 94 g. of dinitrogen tetroxide, and 314 g. of diethyl ether, requiring 1 hour's absorption time at 0°. Removal of ether and excess of tetroxide left 126 g. of product (almost theoretical for $C_4H_8O_4N_2$), which, after being stirred successively with 400, 120, and 60 c.c. portions of water, gave 61 g. of insoluble oil. The aqueous layers yielded 32·1 g., b. p. 56—62°/*ca.* 1 mm., of 1-nitrobutan-2-ol (Found after redistillation: C, 39·9; H, 7·8;

N, 12·0. Calc. for $C_4H_9O_3N$: C, 40·3; H, 7·6; N, 11·8%), and only 1·8 g. of distillation residue. No solid could be isolated from the insoluble oil on cooling in methyl alcohol to −70°, and, after being dried by distillation with benzene, it gave 47·5 g. boiling over a wide range and 3·0 g. of residue. Two further distillations gave 1 : 2-dinitrobutane, b. p. 90—92°/1 mm. (Found: C, 31·9; H, 5·3; N, 19·0. $C_4H_8O_4N_2$ requires C, 32·4; H, 5·4; N, 18·9%).

2-Butylene. The quantities used were 51·9 g. (22·2 l.) of 2-butylene, 197 g. of dinitrogen tetroxide, and 365 g. of ether, requiring 1½ hours' absorption time at 0°. Removal of ether and excess of tetroxide left 139 g. of product (practically theoretical for $C_4H_8O_4N_2$). Extraction successively with 500 and 100 c.c. of water left 58 g. of insoluble oil. Treatment of the aqueous layers as before gave 35·1 g. of 2-nitrobutan-3-ol, b. p. 60—61°/1 mm. The insoluble oil was dissolved in 88 g. of alcohol and cooled to −70°; crystals then separated. All but 2·7 g. disappeared into the filtrate on warming to room temperature. This solid, after recrystallisation from methyl alcohol, melted at 48—49° (Found: C, 32·6; H, 5·4; N, 18·8%). The solvent was removed from the filtrate under reduced pressure, the residual oil dried with benzene, and then distilled under reduced pressure to give 38·5 g., b. p. 64—92°/*ca.* 1 mm., collected in fractions, the higher-boiling part of which gave a further 1·1 g. of the solid form on cooling in methyl alcohol. Redistillation of the remaining oil gave liquid 2 : 3-dinitrobutane, b. p. 76—77°/<1 mm. (Found: C, 32·5; H, 5·6; N, 18·9%).

Properties and Characterisation of Products.—1 : 2-*Dinitrobutane* (IX). This is a colourless liquid, b. p. 90—92°/<1 mm. Like 1 : 2-dinitropropane (Part III, *loc. cit.*) it has one asymmetric carbon atom and has not been obtained solid at room temperature.

Reduction to 1 : 2-diaminobutane was carried out as for 1 : 2-dinitro*iso*butane. From 0·447 g. of (IX) in 30 c.c. of glacial acetic acid in the presence of 0·025 g. of Adams's platinum catalyst at 100 atm., 0·233 g. of diamine dihydrochloride was obtained, m. p. 182° (Found: N, 17·4; Cl, 43·8. Calc. for $C_4H_{12}N_2,2HCl$: N, 17·4; Cl, 44·1%), yield 48%. The dipicrate was prepared by adding dihydrochloride (0·0325 g.) in water (5 c.c.) to picric acid (0·10 g.) in water (70 c.c.); 0·072 g. of dipicrate then crystallised, m. p. 244·5° (decomp.) (Found: C, 35·5; H, 3·9; N, 20·0. Calc. for $C_4H_{12}N_2,2C_6H_3O_7N_3$: C, 35·2; H, 3·3; N, 20·5%).

Formation of propaldehyde. The nitro-olefin solution, prepared by adding (IX) (0·75 g.) to potassium hydroxide (0·2 g.) in water (5 c.c.), was added dropwise to a boiling solution of potassium permanganate (2-g.) in water (40 c.c.) under reflux in a stream of carbon dioxide. The issuing gas was passed to a bubbler containing 2 : 4-dinitrophenylhydrazine in 2N-hydrochloric acid. After 1 hour the propaldehyde was allowed to distil into the bubbler and the 2 : 4-dinitrophenylhydrazone formed recrystallised from alcohol (Found: C, 45·9; H, 4·4; N, 24·1. Calc. for $C_9H_{10}O_4N_4$: C, 45·4; H, 4·2; N, 23·5%).

1-*Nitrobutan-2-ol* (X). This is a colourless mobile liquid, b. p. 60—61°/<1 mm. It is identical with the synthetic material (Jones and Kenner, *loc. cit.*).

1-*Nitro*-1-*butylene formation* via *acetate.* The acetate was prepared in 86% yield by interaction of (X) and acetyl chloride. It had b. p. 62°/<1 mm. (Found: C, 45·1; H, 6·8; N, 9·0. Calc. for $C_6H_{11}O_4N$: C, 44·7; H, 6·8; N, 8·7%). The acetate (5 g.) was heated with potassium carbonate (0·1 g.) at 80°/100 mm., and then distilled at 20 mm. to give the nitro-olefin which, after being washed to remove acetic acid and dried ($CaCl_2$), distilled at 65°/19 mm. (Found: C, 47·4; H, 6·7; N, 13·9. Calc. for $C_4H_7O_2N$: C, 47·5; H, 6·9; N, 13·9%).

2 : 3-*Dinitrobutane* (XI). This exists in two forms, a solid, m. p. 48—49° (Angeli and Alessandri, *loc. cit.*, give m. p. 41°), and a liquid, b. p. 76—77°/<1 mm. Since (XI) has two asymmetric carbon atoms, the solid is possibly the *meso*-form and the liquid the *dl*-form. The diamine dihydrochloride and the dipicrate of the diamine from the solid form have melting points which differ from those of the derivatives from the liquid form.

Reduction to 2 : 3-*diaminobutane.* (a) Reduction of the solid form (0·441 g.), as before, gave 0·65 g. of crude dihydrochloride, which, after recrystallisation from alcohol, had m. p. 240—241° (Found: N, 17·7; Cl, 42·6%). The dipicrate, prepared as above, had m. p. 230° (decomp.) (Found: C, 35·3; H, 3·2; N, 20·4%).

(b) The liquid form (0·449 g.) gave 0·192 g. of *dihydrochloride*, which was washed with alcohol (Found: N, 17·5; Cl, 43·7%). This dihydrochloride was much less soluble in acetic acid and alcohol than that obtained from the solid and had a much higher melting point, darkening at 275—280°. The dipicrate also had a higher melting point, darkening at 240—250°. The acetic acid remaining after separation of the above dihydrochloride gave a further 0·068 g. of the dihydrochloride obtained from the solid form, confirmed by m. p., mixed m. p., and formation of identical dipicrate.

Formation of acetaldehyde. (a) The solid form (0·51 g.) was dissolved in an aqueous solution of potassium hydroxide (0·46 g.) and added to water (40 c.c.) under reflux. The reaction was carried out in a stream of nitrogen and the acetaldehyde vapour passed into 2 : 4-dinitrophenylhydrazine in 2N-hydrochloric acid. The dinitrophenylhydrazone was recrystallised from alcohol (Found: C, 42·0; H, 3·0; N, 25·3. Calc. for $C_8H_8O_4N_4$: C, 42·8; H, 3·6; N, 25·0%).

(b) The liquid form (0·75 g.) treated as for the solid with 0·60 g. potassium hydroxide gave acetaldehyde 2 : 4-dinitrophenylhydrazone (Found: C, 42·6; H, 3·6; N, 25·3%).

2-*Nitrobutan-3-ol* (XII). This, when pure, is a colourless mobile liquid, b. p. 60—61°/<1 mm.

2-*Nitro*-2-*butylene formation* via *the acetate.* 2-Nitrobutyl 3-acetate, b. p. 61°/1 mm., was prepared in 89% yield by interaction of the nitro-alcohol and acetyl chloride. By heating 5 g. with 0·1 g. of potassium carbonate at 70°/25 mm. for 2 hours and distilling at 14 mm., followed by washing, drying and distilling, 2-*nitro*-2-*butylene* was obtained, b. p. 58°/18 mm. (Found: C, 49·6; H, 6·8; N, 13·5. $C_4H_7O_2N$ requires C, 47·5; H, 6·9; N, 13·9%).

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15. *The Structure of Molecular Compounds. Part IV. Clathrate Compounds.*

By H. M. Powell.

It is shown that molecules may be firmly united to each other without the operation of strong attractive forces between them but through the enclosure of one by the other, of both by each other, or in more complex ways. The space arrangements are such that it is impossible to separate the different components without overcoming the strong attachment, *e.g.*, by hydrogen bonds of the molecules of one component only which are thus joined to form an enclosing structure around the others. The conditions of formation, the compositions, and some properties of such compounds are discussed. Among the examples given are those in which either two or more identical giant molecules interpenetrate and enclose each other, and others in which cage structures of suitable form imprison molecules of a second kind to give compounds of either fixed or variable molecular ratios. It is suggested that they should be named " clathrate " compounds (" clathratus," enclosed or protected by cross bars of a grating).

In addition to compounds whose existence is explained by the union of the components by chemical bonds of various types there are molecular compounds which do not require these bonds. In this class of compound molecules interact by attraction of their permanent dipoles, through dipole induction effects and through dispersion forces in varying degrees of importance (Briegleb, " Zwischenmolekulare Kräfte und Molekülstruktur," 1937). In crystalline molecular compounds the whole-number ratio of the two components, so far as it holds, is in part a packing effect, *i.e.*, it arises when the requirements of molecular size and shape can be satisfied by the formation of a crystalline compound containing the components in some simple ratio (Parts I and II, *J.*, 1943, 153, 435). The present communication deals with a further general type of union which may lead to the formation of molecular compounds, sometimes of simple formula, through an association of different molecules without chemical combination in the usual senses, and although interactions of the other kinds mentioned above may play a rôle in particular cases, it is not *essential* for this type of union that there should be attraction between the molecules which are firmly held for other reasons.

A possible type of intermolecular compound formation involves the complete enclosure of a molecule by one or more molecules of another component in such a way that it cannot escape from its position unless strong forces holding its surroundings together are overcome. The enclosed molecule must then remain in association with its surroundings as firmly and as permanently as the parts of these surroundings are held to each other. This provides a means of uniting together different substances which may have very little attractive interaction. The form of enclosure required for such a compound is that of finite atomic groups or infinitely extended complexes that contain spaces of size great enough to hold a molecule of the second component. The spaces must also be bounded in such a way that escape of the enclosed molecule is prevented.

In order to determine the circumstances in which such a compound might be produced it is necessary to consider the conditions of formation of the surrounding structure which is to enclose the second component. Since it is assumed that there is to be little attraction between the enclosed and enclosing members, the compound is to be expected only when there is some special reason for the formation of the particular type of cage structure by the one component. In many materials the aggregation of the constituents is such as to give the best possible filling of space. Thus, in liquid mercury the atoms have on the average as many neighbours as possible, and many crystalline structures, *e.g.*, those of many metals, minerals, and complex ionic compounds, are formed of closest or nearly closest packed arrangements of spheres. Similarly, in many molecular crystals it is observed that molecules of very diverse shapes are arranged with the projections of one molecule fitting into the indentations of others so as to achieve a good degree of space filling; for adjacent atoms of neighbouring molecules not only are there no interatomic distances less than the van der Waals radius sum but also there are no distances greatly in excess of these equilibrium distances, *i.e.*, large vacant spaces are avoided. In molecular crystals this space filling is brought about by the residual attractions which bring the molecules to a state of lowest potential energy when the packing is as close as possible. However, in structures where interatomic forces of several kinds are operative close packing may not be attained. Forces much stronger than the van der Waals attractions may impose an arrangement which is more open. Any attempt to alter the structure against these forces causes an increase of potential energy which will not be compensated by the comparatively small diminution due to a closer packing. In water the strong interaction through hydrogen

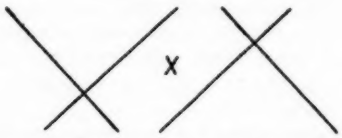
atoms between one oxygen atom and its neighbours leads, owing to the directed character of the link, to a structure in which each water molecule has on the average about four neighbours only, and thus water has an open structure. For similar reasons open structures are found in the crystalline state, *e.g.*, in ice, owing to the directed OH . . . O bonds, in diamond on account of the directed tetrahedral C–C covalent bonds, and in α-resorcinol (Robertson, *Proc. Roy. Soc.*, **1936, 157, 79**) owing to a combination of two effects, the general shape of the comparatively rigid molecule as a whole and the requirement that the molecules shall be linked together through as many hydrogen bonds as there are hydroxyl groups, these hydrogen bonds being restricted to directions at approximately the tetrahedral angle to the C–O bonds.

Similarly, in ionic crystals the requirements of anion–cation contact may outweigh other effects, and for particular radius ratios may impose a structure of low co-ordination number which does not very effectively fill space.

The open structures already mentioned do not, however, enclose spaces of any great dimensions such as might contain a second atom or molecule. To obtain such large spaces it is necessary to increase the dimensions of the structural components, *i.e.*, instead of single atoms, extended groups of linked atoms must be held by strong attractive forces to their neighbours.

Some open structures result, in crystalline minerals, from the rigid form of silicon–oxygen frameworks and in the zeolites (Taylor, *Z. Krist.*, **1930, 74, 1**) there are spaces large enough to contain other loosely bound material. These spaces, however, are channels rather than complete enclosures, and the second component may be removed or interchanged for other materials since there is access to the surface of the crystals. Similar structures might be built up by use of the rigid linear metal–CN–metal sequence found in a number of complex cyanides. This

FIG. 1.



(*Schematic only.*) *The two molecules of arbitrary shape are imagined restricted by their neighbours to movement to right and left only. They are shown at the minimum separations possible between their projecting ends. Space is left for another small component at* X.

may result in the formation of infinitely extended cage structures in which the cage bars have the length M–CN–M of 5 A. or more and are disposed in directions determined by the metal M, *e.g.*, octahedral M bonds may result in cube-shaped cages as probably occurs in Prussian-blue.

Structures of a more open character would result if a longer linear sequence of atoms were used as the cage bar, or if the bonds were disposed tetrahedrally around the metal to form diamond-like structures, but this does not necessarily mean that the conditions for enclosure of other molecules are thereby attained, since access to the outside of the enclosure will be made easier through a corresponding enlargement of the holes available for escape. In general, it may not be easy to construct by covalent bonds alone cages having suitable spaces combined with holes small enough to prevent escape of the other molecules that could occupy the spaces. A further difficulty is that of ensuring, in the conditions of formation of the bonds, that there is a second molecule in the right place to be trapped at the time when the cage is closed.

These difficulties may be overcome by selecting as the cage-forming components atoms covalently linked to form groups of appropriate superficial extension and binding each group firmly to its neighbours, at two or more points, by means other than covalent linkages. In two cases such an arrangement leads to inter-group cavities. In the first, the shape of the group is such that no packing can be made without this happening, as indicated schematically in Fig. 1. Rigid projecting portions of molecules or complex ions are so disposed that when closer approach is stopped by contact of these projections there remain spaces able to contain another molecule at van der Waals distances from its surroundings although these spaces cannot be used for better packing of the groups that enclose them. In the second, the packing is complicated by other conditions such as the directional requirements of hydrogen bonds linking the groups, and this may lead to cage structures similar to those resulting from covalent links alone.

This linking of the cage structure through covalencies combined with some other form of binding has many advantages. The component parts of the cage structure may be capable of separate existence as molecules or complex ions. They may be selected to be of suitable size and shape and their points of attachment to each other determined by the position of the

hydrogen-bond-forming groups, or in the case of complex ions, by appropriate selection of the oppositely charged ions. Here, instead of a linear group of atoms as a cage bar, there is the whole covalently linked molecule or other group of atoms that may project over the faces of the cage. In this way large holes of exit may be blocked.

A molecule to be enclosed must be in the right place when the cage is closing and for a cavity formed without an enclosed molecule the difficulty of getting one in would be the same as that of getting it out. For a cage formed by covalencies alone it is not easy to avoid this, but if the cage structure is formed in solution or on a crystal surface by the ordered arrangement of a number of molecules or groups bound to each other at many points there will be a time before the space is completely sealed when the space is open to penetration by solvent or other solute molecules which may be present in relatively large concentration. The cage is also capable of re-opening, *e.g.*, when molecules or ions pass back into solution, and if the enclosed space is large the probability that the cage will close on an unoccupied space will be small.

For an enclosed molecule to leave its enclosure it must overcome the attraction between itself and the cage, but even if it were possible for there to be no attraction, escape will be prevented by another process for some types of cage and enclosed molecule. When this molecule approaches a possible hole of exit its outward passage will be opposed by the repulsive forces that arise when any two atoms approach closely. These forces which are responsible for the approximate constancy of the effective atomic radii rise rapidly as atoms approach closer than the equilibrium distances. If the molecules forming the cage are subject to strong mutual attraction they will not be pushed apart readily, and if the holes of exit are sufficiently small the enclosed molecule will therefore be repelled inwards.

The process of escape of an enclosed molecule may be regarded as a type of dissociation reaction in which the rate of reaction depends on the activation energy. This activation energy is a measure of the work required to bring the enclosed molecule to the middle of an exit hole from which it may pass with equal ease into or out of the cage. It will vary greatly with the structural character of the molecular cage and the enclosed molecule and may be different for different holes of the same cage. For it to be high the requirements are that the escaping molecule must pass appreciably nearer than the normal van der Waals distances to the atoms forming the cagework, and it must be impossible for the component parts of the cage to be moved apart except against large resisting forces due to their attachment to each other. Whatever the precise distribution of energies among the enclosed molecules it is clear that the fraction of them having the amount necessary for escape will be very small if the activation energy is several times the average energy for the temperature concerned. In the extreme case in which all escape is effectively prevented except in conditions which destroy the cage structure a new type of compound is distinguished. The dissociation behaviour of this type of compound, once formed, is not determined by the attraction between the different molecules and the ease of dissociation bears as little relation to this attraction as the velocity of a reaction does to the affinity.

There may thus arise a structural combination of two substances which remain associated not through strong attraction between them but because strong mutual binding of the molecules of one sort only makes possible the firm enclosure of the other. It is suggested that the general character of this type of combination should be indicated by the description " clathrate " compound—" clathratus," enclosed or protected by cross bars of a grating.

For a full description the detailed structural arrangements must be given for each compound, but a convenient representation of constitution may be made by encirclement formulæ of the type (*a*), C giving the composition of the cage, M that of the enclosed component. When

(*a*.)

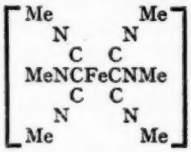
(*b*.)

the cage is an infinitely extended complex in a crystal the formula may be written as in (*b*). This method of formulation is easily extended to include other complexities as discussed below. Some examples of clathrate compounds will be described before the modes of formation, composition, and properties are considered further.

Hexamethylisocyanidoferrous chloride trihydrate (I). The complex ion (II) has six nearly linear $-CN\cdot CH_3$ arms disposed octahedrally about the central iron atom. In the crystal structure (Powell and Bartindale, *J.*, 1945, 799) these ions are packed as closely as is possible in hexagonal layers with their terminal methyl groups in effective contact at 3·9 A. in any layer.

The closest packing of these layers is obtained by placing the downward-projecting arms of one complex ion to fit into the spaces between the three upward-pointing outspread arms of the ion

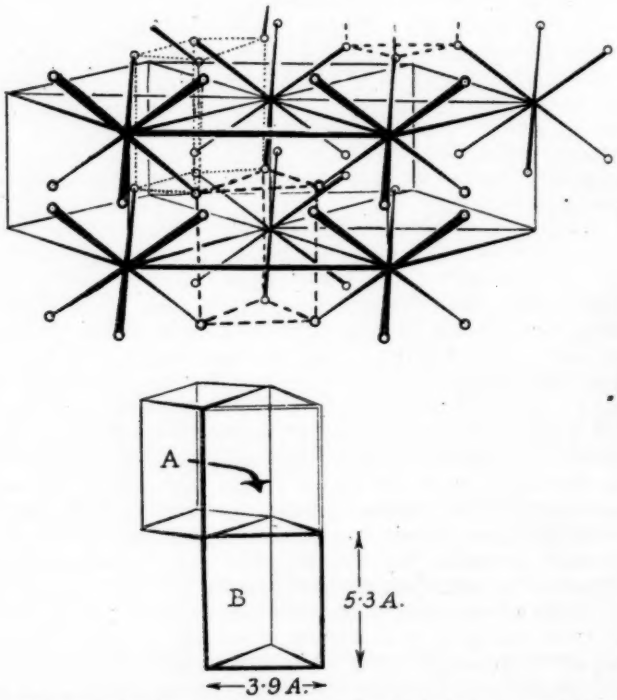
(I.) $\left\{ [Fe(CN\cdot CH_3)_6]Cl_2 \cdot 3H_2O \right\}_n$



(II.)

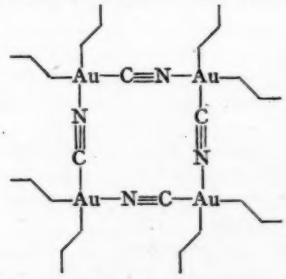
below with a CH_3–CH_3 separation of 3·7 A. The general arrangement is shown in Fig. 2. Although it is packed as closely as possible, this complex group cannot fill the space owing to its shape, which is determined by the bond lengths and angles. It is important that the projecting

FIG. 2.



Hexagonal packing of the complex ions $[Fe(CNMe)_6]$. *Small circles represent the terminal methyl groups. The spaces left when the methyl groups are in effective contact are shown by the broken lines above and in parallel positions below.*

portions of the molecule or complex ion that bring this about shall not be capable of rotations about single bonds in such a way that they will fold into positions that give a better packing.



(III.)

The awkward shaped molecule (III) of di-*n*-propylmonocyanogold might be expected to give a similar open structure, but in its crystals (Phillips and Powell, *Proc. Roy. Soc.*, 1939, *A*, **173**,

147) rotation of the propyl groups about the single bonds to the gold atoms makes it possible to form a complicated structure of low symmetry which, however, does not leave any large spaces. Such folding cannot occur with the complex ion (II) since the arms are linear. The spaces it leaves in the structure are of two kinds indicated in Fig. 2 by *A* and *B*. There is a set of these spaces with contiguous surfaces as shown in the lower part of the figure. To leave a space, an upward-moving atom must approach the atoms at the corners of the space to within 2·6 A. if it emerges from *A* or 2·2 A. if it emerges from *B*. Sideways movement from one space to another or through the surface of the crystal in the direction of the arrow does not require a closer approach than 3·5 A. to the terminal methyl groups of the octahedral complex ion. Movement could occur through all three side faces of the *B* space but only through two opposite faces of the *A* spaces, the other two sides being blocked by the octahedral complexes.

In the salt under discussion the three *A* spaces per unit cell are occupied by two chlorine ions and one of the water molecules, the arrangement being disordered so that for the structure as a whole each *A* position has statistically $\frac{2}{3}Cl + \frac{1}{3}H_2O$. The remaining two water molecules occupy the two *B* positions of the unit cell. The interionic attraction binds the complex ions and chlorine to form a strong cage structure and the water molecules cannot escape upwards, since their movement is barred by the methyl groups, or sideways, because the adjacent *A* spaces contain firmly fixed chlorine ions. It is observed that the water in these crystals can be removed only to a very small extent and this may be attributed to the imprisoning action. On prolonged heating of the crystals at a temperature slightly below 100°—higher temperatures are impracticable owing to decomposition of the substance with loss of methyl chloride—slight dehydration occurs, the crystals are seen to be crossed by faint white bands on the sides of the hexagonal prism, and they fall apart into slabs parallel to the hexagonal base. This suggests that the water may to a small extent emerge sideways but not upwards. This sideways movement is very much restricted since a molecule of water, having moved from *A* to *B* will usually find the two neighbouring *A* positions occupied by chlorine ions which prevent its further movement. The emergence with great difficulty of a small amount of water may be due to some molecules making their way through a few unblocked routes. There does not appear to be any other special reason why the water should be so tenaciously held in this compound; there is no evidence that it is strongly attached to any part of its surroundings, and the behaviour is therefore attributed to the imprisoning action.

Compounds of quinol with small molecules. Crystalline compounds of formula $M,3C_6H_4(OH)_2$, where M may be SO_2, H_2S, HCN, HCl, HBr, $H{\cdot}CO_2H$, $CH_3{\cdot}OH$, or $CH_3{\cdot}CN$, have been investigated by Palin and Powell (Part III, *J.*, 1947, 208). The imprisonment of one component by another is shown in a twofold manner in these structures. The quinol molecules link through hydrogen bonds directed at approximately the tetrahedral angle to the C–O bonds to form infinitely extended three-dimensional cageworks. Owing to the size of the covalently bound group of atoms connecting the two points of hydrogen bond attachment of each molecule, the resulting structure (see Fig. 13, Part III) is an extremely open one, and this extended cage structure would have a density of only 0·61 g./c.c., as calculated from its composition and dimensions. So great is the available space and so large the holes of entry to the cagework that it is possible to arrange a second identical cagework completely interpenetrating the first. This gives an association of two giant molecules which have no direct linkages but which are inseparable without the breaking of hydrogen bonds. Both molecules imprison the other by multiple enclosures. The constitution may be denoted by the encirclement formula (*c*). The

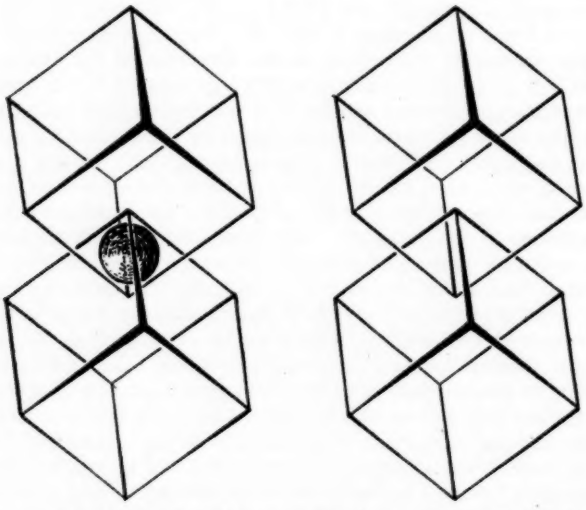
$$\left\{1\tfrac{1}{2}C_6H_4(OH)_2\big(\big)1\tfrac{1}{2}C_6H_4(OH)_2\right\}_n \quad (c.)$$

$$\left\{1\tfrac{1}{2}C_6H_4(OH)_2\big(SO_2\big)1\tfrac{1}{2}C_6H_4(OH)_2\right\}_n \quad (d.)$$

interlocked rings denote mutual enclosure of two identical cageworks; the subscript *n* outside the brace shows that the cages are infinitely extended and that there is multiple enclosure of each cagework by the other. This arrangement of interpenetrating molecules still leaves unoccupied spaces able to contain the small molecules M. These spaces are bounded by parts of both the quinol frameworks and there are no holes of exit through which the enclosed molecule may emerge without close approach to the atoms of the framework. The general character of the enclosing action may be seen from Fig. 3. The sulphur dioxide, or other molecule M, is very firmly retained in spite of its volatile character in the free state, but it is readily liberated by any process that destroys the framework, *e.g.*, by addition in the cold of liquids that dissolve

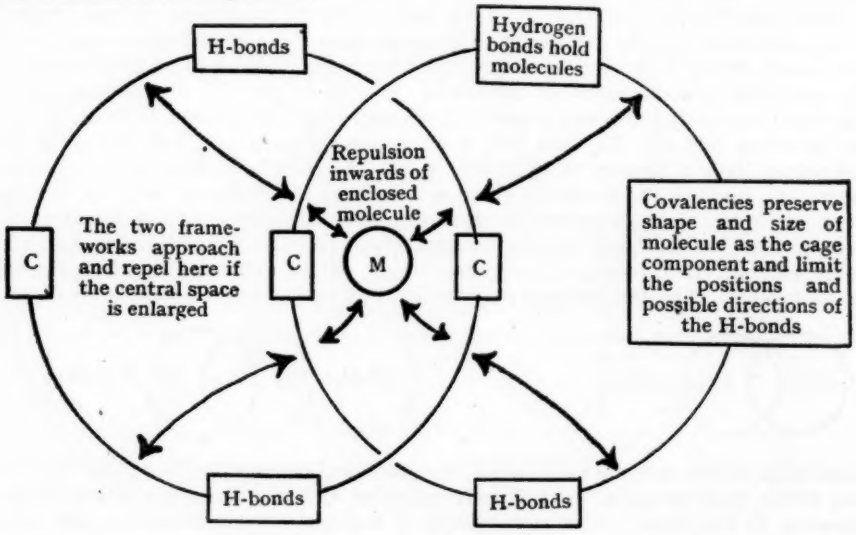
quinol, by melting, or to a small extent by grinding the crystals. The formula of the compound is determined by the ratio of available cavities to the amount of cage material. The constitution may be represented by the formula (*d*) which expresses the composition, and the

FIG. 3.



Schematic representation of interpenetration of two cage structures. The quinol molecules are to be imagined as the edges of the cage. In the crystalline structure the corresponding cages are extended indefinitely in three dimensions, six quinol molecules being joined together at each corner of the figure. In the crystal the corners of one cage system fall at the centres of the other but in this figure they have been displaced in an arbitrary manner for greater clarity. On the left a small molecule is shown trapped between the two cages.

enclosure simultaneously by two infinitely extended frameworks, although it cannot express the detailed structural arrangements.


H-bonds
Hydrogen bonds hold molecules
Repulsion inwards of enclosed molecule
The two frameworks approach and repel here if the central space is enlarged
C
C
M
C
Covalencies preserve shape and size of molecule as the cage component and limit the positions and possible directions of the H-bonds
H-bonds
H-bonds

(*e*; C = covalencies.)

The precise nature of the restriction on emergence of the sulphur dioxide molecule is considered further in view of the explanation to be given for the next substance mentioned below. As indicated diagrammatically in (*e*), the enclosed molecule could escape by pushing apart the two independent portions of its cage, against their van der Waals attraction. This may be large

but an indirect effect of greater importance is that the attempt to enlarge the holes of exit in this way necessarily brings the cages into closer contact in other places. The resulting large repulsions, which prevent the enlargement of the holes, are in their turn only possible if the hydrogen bonds hold the quinol molecules firmly together. Some bending of the hydrogen bonds is possible, as shown by the small differences in the shape of the cage for different enclosed molecules, but only a complete break will release the enclosed molecule. Finally, the hydrogen bonds are retained in their positions by the rigid structures of the covalently linked quinol molecules.

Quinol–formic acid–carbon monoxide. In an attempt to prepare formyl derivatives of quinol by heating this substance with formic acid in a sealed tube, Mylius (*Ber.*, 1886, **19**, 999) obtained a crystalline product of remarkable properties. On solution in cold water or other solvent it immediately liberated carbon monoxide and quinol could be recovered from the solution. It melted at 170° also with liberation of carbon monoxide. That it is not simply a compound of carbon monoxide and quinol was shown by analysis, by failure to prepare it when the mixture was heated in the same way but with an attachment to absorb water resulting from the decomposition of the formic acid, and by the detection of a small quantity of formic acid in it.

The properties of this substance may now be explained if it is assumed to be a clathrate compound of type $M,3C_6H_4(OH)_2$, where M is partly formic acid and partly carbon monoxide. Formic acid alone will form a similar compound but in the conditions used carbon monoxide will not. The absorption of water may have led to the decomposition of all the formic acid so that no medium remained in which quinol and carbon monoxide could be dissolved, but it is of some interest to consider an alternative explanation. It might be that a molecule small enough to escape from the cavities and therefore incapable of this type of compound could nevertheless be retained by a cagework which had some of its cavities already occupied by larger molecules such as those of formic acid, which block the exit of the smaller ones. From the fact that there is a measurable energy of activation for the diffusion of nitrogen into some zeolites which contain already a certain amount of water whereas there is no appreciable energy of activation for the same zeolite after more complete removal of the water (Emmett and DeWitt, *J. Amer. Chem. Soc.*, 1943, **65**, 1253), it has been concluded that water molecules fixed in zeolite channels may impede the inflow of nitrogen. Enclosure compounds are imaginable in which a similar obstacle prevents the emergence of a small molecule. The carbon monoxide molecule, not much smaller than that of hydrogen cyanide, which forms a compound, may be retained in the ordinary way without the need for formic acid but the implications of the alternative explanation are mentioned below since they may apply to other compounds.

The analytical results of Mylius (*loc. cit.*) show a variable carbon content. The hydrogen content does not vary in a systematic way with the carbon percentage and is approximately constant with a mean value of 5·3% as shown below for six different samples :

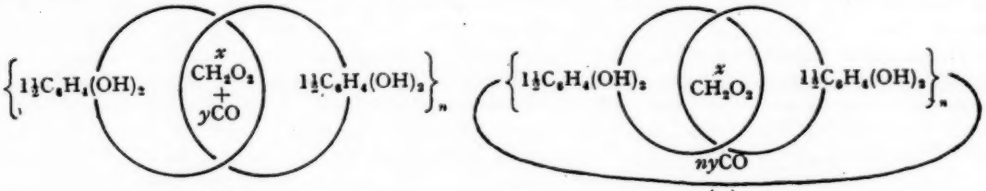
C, %	61·29	62·08	62·10	62·61	62·63	62·93
H, %	5·30	5·33	5·26	5·29	5·25	5·56

The requirements of the formula $3C_6H_4(OH)_2,(1-a)CH_2O_2,aCO$, *viz.*, C, 60·6—63·7, H, 5·32—5·03 as a changes from 0 to 1·0, will account for the carbon percentages but not for those of hydrogen. The composition may be derived in the following way. It is supposed that the crystals are composed of quinol frameworks similar to those of the compounds previously mentioned, including the compound of quinol with formic acid. Between the frameworks some formic acid is enclosed, but in the temperature conditions of the preparation a certain proportion of the formic acid molecules are undergoing decomposition into carbon monoxide which may be retained by the further deposition of material on the crystal surface. Once enclosed by its own cage and possibly by the next deposited layer containing formic acid, it is retained in the manner described above, but there is a chance for it to escape before the next layer is deposited. If it escapes in this way after the cage has formed, the space cannot be filled by a formic acid molecule since the possible hole of entry is too small for this larger molecule. The resulting crystal therefore will have the composition $3C_6H_4(OH)_2,xCH_2O_2,yCO,z(O)$ where (O) represents a vacant space, and $x+y+z=1$. The introduction of vacant spaces makes it possible to vary the carbon content without appreciable variation in the hydrogen proportion, *e.g.*, the hypothetical series $3C_6H_4(OH)_2,(1-a)CH_2O_2,\frac{1}{2}aCO,\frac{1}{2}a(O)$ gives C ($a=0$) 60·6, ($a=\frac{1}{2}$) 62·5, ($a=1$) 64·5; H ($a=0$) 5·32, ($a=\frac{1}{2}$) 5·28, ($a=1$) 5·23. Mylius carried out determinations of the carbon monoxide and formic acid in addition to elementary analysis and his results can be explained on the formula $3C_6H_4(OH)_2,xCH_2O_2,yCO,z(O)$ with $x=0{\cdot}45$, $y=0{\cdot}125$, $z=0{\cdot}425$. This gives C, 62·9, H, 5·34 (Mylius: 62·93, 5·56) and for CO, 1·0, formic acid, 5·85 (Mylius: 1·0 and 5·7—5·9%). The complete figures are not available for all samples but the carbon and hydrogen contents may be explained by suitable variations of x, y, and z.

The large proportion of vacant spaces is not incompatible with the notion that the egress of the small carbon monoxide may be prevented by the presence of the larger formic acid. The only hole available for exit is the hexagon of side 2·7 A. formed by the hydrogen-bonded oxygen atoms (see Part III), and to escape from its enclosure a carbon monoxide molecule would be expected to pass by way of a channel parallel to the *c* axis of the crystal through a succession of such hexagons. A blocking of these escape routes may clearly be made with far less than the 45% occupancy of the cavities by formic acid. The figures as calculated show roughly half the spaces occupied by formic acid molecules, and of the rest about three-quarters are vacant and one-quarter occupied by carbon monoxide. A simplified picture of the enclosure in the channel may be shown by the sequence CH_2O_2 blank CH_2O_2 blank CH_2O_2 blank CH_2O_2 CO CH_2O_2 blank CH_2O_2 . . . which represents one of the possible ways of arranging the contents of a succession of cavities parallel to the *c* axis of the crystal. Other arrangements are possible, and although there is a certain probability of a carbon monoxide molecule being contained in a cavity which itself adjoins an empty cell, it is in any case bounded somewhere on both sides by occupied cells and there is a good chance that its two immediate neighbouring cells will both contain formic acid molecules.

Even if the explanation does not apply in the present case, it serves to show that by the process described it should be possible to combine together the most diverse substances provided that there is a means of getting the required molecules into position when the crystal is formed.

The quinol–formic acid–carbon monoxide compound is represented by the formula (*f*) if the formic acid is not necessary, but if the carbon monoxide is only retained by the combined caging effect of quinol and formic acid the alternative representation is (*g*). This shows a



crystal complex of formula $\{3C_6H_4(OH)_2,xCH_2O_2\}_n$ which as a whole encloses *ny*CO. The formic acid is shown enclosed by the interpenetrating quinol cageworks but also as an essential part of the structure which encloses the carbon monoxide.

Modes of formation of clathrate compounds. In the examples already discussed the essential condition that the cage shall form around the other molecular component is achieved by the building up of the cage bit by bit from small components capable of separate existence in the solution which also contains a large concentration of the molecules to be enclosed. The sulphur dioxide–quinol compound cannot be made directly by contact of its components at room temperature in the dry state. Apart from any other considerations this limits the possible partners in the compounds to those that can be present in sufficient concentrations in the same solution. High pressures might be used to increase the concentration of the second component, and preliminary experiments have shown that this method is successful in bringing about combination with a gas that does not form a compound at ordinary pressure owing to its small solubility. This suggests the possibility of forming a compound with an inert gas, *e.g.*, by crystallising quinol from a solution saturated with krypton at high pressure.

A method of preparation possibly applicable in a few special cases would be the formation of a compound from a substance that may be enclosed, followed by decomposition of the enclosed material. Thus the enclosed molecules might be decomposed by the action of heat, ultra-violet light, or *X*-rays, and, if the necessary condition is fulfilled that the cage remains unaffected, a molecule which could not otherwise be induced to enter the cage might be formed and retained in it.

Composition of clathrate compounds. The composition of these compounds may be reduced to a basic formula (*h*), which gives the amount of cage-forming material for every available cavity and the composition of the material enclosed per cavity, but ignores structural details which for some purposes may not be of great importance and in any case are only imperfectly described by more complex encirclement formulæ. In the formula *n*M there may be: (*a*) a whole number *n* of molecules of the second component M, (*b*) any fractional amounts of two or more enclosed molecules that together add up to a whole number, (*c*) fractional amounts as in (*b*) with the limitation that one of the enclosed molecules must be present in some minimum proportion needed to trap the other

(*h.*)

enclosed components, (*d*) fractional amounts that do not add up to a whole number. Case (*d*) may arise through some of the cavities being unoccupied. It could also occur in a structure with sufficiently large cavities occupied by more than one molecule when the determining factor would be the volume available and $M = X_nY_m$ where X and Y are moleules enclosed such that $(n + m)$ is not integral but the effective volume of X_nY_m is roughly constant.

For a given cage the type of molecule M is determined by volume considerations, not by the chemical nature of the molecule. In the examples given, the total volume of the enclosing parts is considerably greater than that of the enclosed component. Cavities which arise only from the impossibility of close packing of awkward shaped molecules must be smaller, and usually will be considerably smaller, than the cage-forming molecules themselves, and the presence in a molecular compound of a relatively small amount of one component, especially if the molecular ratio of the two components has no relation to the conceivable unions by other means, provides grounds for suspecting that the compound is of the clathrate type.

For cavities which arise from the directed character of the bonds linking the cage structure, the volume ratio of enclosed to enclosing material is not necessarily so small. Thus the material of the single quinol framework structure mentioned above has a less volume than the total available for enclosed material, as is clear from its enclosing not only an identical framework but small molecules in addition.

There will be a lower as well as an upper limit to the size of enclosed molecule that enters into combination with a given cage since a sufficiently small molecule would be able to pass through the escape holes without meeting the inward repulsion which is necessary to stabilise the compound. This explains the failure of water to form a compound with quinol. It might have been supposed that the various molecules which may be enclosed by quinol were attached to the framework, *e.g.*, by hydrogen bonds, but if this were the explanation water should be more firmly attached than some of the others, *e.g.*, hydrogen sulphide. But if any interactions between the cage and its enclosed molecule are insufficient to hold the components in the firm manner observed, and the factor determining permanence is the lack of access to the surface of the crystal, it follows that water is one of the molecules that will not form a compound, since it could pass out of the cage by way of the hexagons of hydrogen-bonded OH groups that link the quinol molecules. To do this it must approach to within 2·8 A. of the oxygen atoms, a distance very little less than the average separation, 2·9 A., of oxygen atoms in water. In contrast, the methyl alcohol molecule, which does not link more firmly to quinol for any other reason, is retained because the van der Waals equilibrium distance $CH_3 \ldots O$ is about 3·4 A. and the outward passage of the molecule is therefore prevented. Quinol crystallised from water forms a structure, not yet determined in detail, different from that found for the 3 : 1 compounds discussed above but containing similar cavities (see below.) This form, α-quinol, with unoccupied cavities, is also obtained from ethanol. In the series HOH, MeOH, EtOH the extreme members do not form the clathrate compound, their molecules being respectively too small and too large. This size factor accounts for the apparently erratic behaviour of quinol in giving compounds with a very varied set of molecules of about the same dimensions although it does not give similar compounds with molecules that are chemically closely related to one or other of the series.

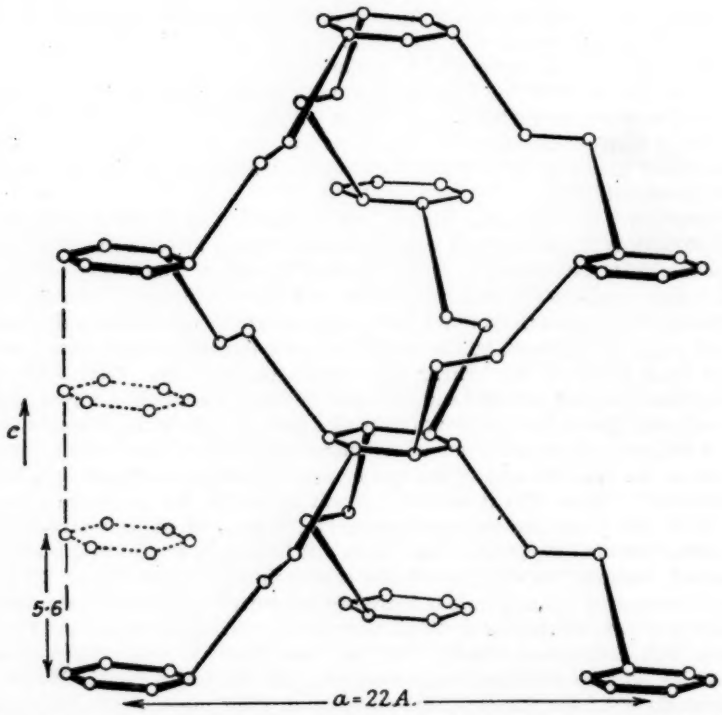
Although structural investigations by physical methods are necessary for final decision, a preliminary assignment of a compound to the clathrate type may be made or rejected from consideration of the properties, molecular ratios, relative volumes of the components, and the behaviour of homologous or closely related substances. Some examples of this process are given below. The first of these is of particular interest since it shows how considerations of this kind may be used to determine what appears at first to be a very complex crystal structure, that of α-quinol itself.

α-Quinol. Quinol crystallised from water or ethanol gives crystals of the α-form which do not contain other enclosed molecules. The dimensions of the hexagonal unit cell are $a = 22{\cdot}07$, $c = 5{\cdot}62$ A. The lattice is not rhombohedral and there are 18 molecules per unit cell, twice as many as in the smallest hexagonal cell that may be chosen for the molecular compounds. The space-group is $C\bar{3}$ (Caspari, *J.*, 1926, 2944). The *a* dimension has no simple relation to that of the previously mentioned series of molecular compounds, but the *c* dimension agrees with those of the molecular compounds as closely as they agree with each other.

The structure is in course of detailed determination but may be predicted from the above facts and the behaviour (described below) with carbon dioxide as composed of independent interpenetrating giant molecules, probably three in number. Each giant molecule imprisons the others. The essential component of the structure is an interlocking group of quinol mole-

cules enclosing cavities similar to those of the 3 : 1 molecular compounds. However, the quinol molecule links through hydrogen-bonded hexagons only at one of its hydroxyl groups, the other hydroxyl group being linked to its neighbours in such a way as to give a more compact arrangement of molecules than that imposed by the large hydrogen-bonded hexagons. There are thus only half as many cavities as in the 3 : 1 molecular compounds, *i.e.*, one cavity to six quinol molecules, and the density 1·33 is accordingly higher than that calculated for the quinol structure of the molecular compounds with vacant spaces, *viz.*, 1·22 g./c.c. The approximate relationship of the interpenetrating molecules may be seen from Fig. 4, and the

FIG. 4.

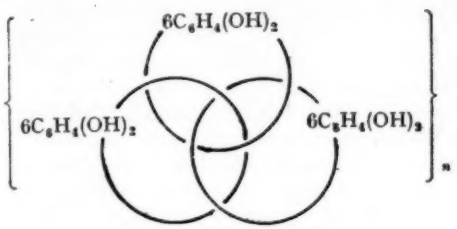


Possible structure for α-quinol. For clarity, only one of the interpenetrating giant molecules is shown, all benzene rings are omitted, and only the essential linkages of the cagework are shown. The small circles denote oxygen atoms. Each quinol is linked through one of its oxygen atoms by hydrogen bonds so that six oxygens form a hydrogen-bonded hexagon from which quinol molecules project alternately up and down. These molecules are denoted by long sloping lines which join the two oxygen atoms of one molecule. The second oxygen links to other molecules through hydrogen bonding but not in the open hexagon form. Enough links are shown to illustrate the formation of a cage structure. The cage is shown as having the height of three unit cells, and two hexagons shown by broken lines indicate the positions from which two structures identical with this cage are to be built up so that they interpenetrate the first cage and each other. Similar structures with different numbers of interpenetrating molecules may be imagined.

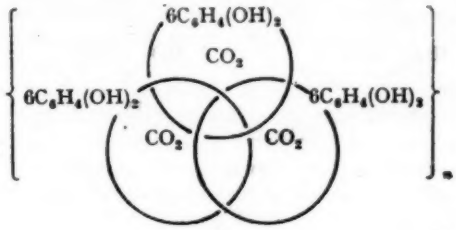
encirclement formula may be written as in (*i*). These diagrams are for three interpenetrating giant molecules but may be easily modified for any other number.

Quinol–carbon dioxide. It appears that clathrate compounds will also form with the α-quinol structure as the cage component. A carbon dioxide compound has been obtained by crystallisation of quinol from a benzene solution in presence of carbon dioxide at more than 50 atmospheres' pressure; it has a variable composition with not more than one molecule of carbon dioxide to six of quinol. Optical and *X*-ray examinations show that it has in the main the α-quinol type of structure, but there are further complexities which are still under investigation. It is a stable solid which liberates carbon dioxide when solvent is poured over it. The encirclement formula is drawn so that each circle passes over both the others and then under both. If the part of the circle which passes underneath at both ends is regarded as taking no part in the enclosure of an area, the state of the carbon dioxide molecules as enclosed simultaneously

by any pair of the framework quinol structures is correctly depicted as in (*j*). Attempts were originally made to obtain a compound of quinol with carbon dioxide, since the size of the carbon



(*i*.)

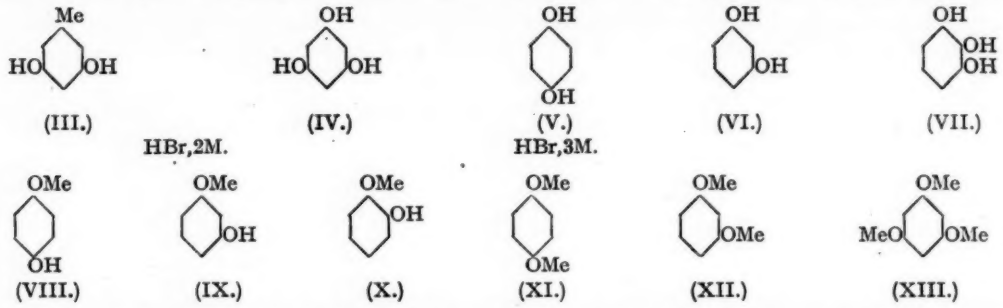


(*j*.)

dioxide molecule seemed favourable and this molecule differs from those already shown to form addition compounds in that it has no dipole moment which might be considered to play some rôle in the interaction of the two components. The general behaviour is outlined here without reference to the complexities mentioned above. At ordinary pressures of carbon dioxide an aqueous solution gives crystals of α-quinol containing no carbon dioxide. This is attributed to the low concentration of carbon dioxide, the quinol adopting the compact α-structure as it does when crystallised from pure water. At high pressures in benzene solution the compound already mentioned is obtained, but at moderate pressures Palin (private communication) has obtained from aqueous solution a compound $3C_6H_4(OH)_2,CO_2$ similar in structure to the sulphur dioxide compound. The first effect of pressure is therefore to increase the concentration of the carbon dioxide in solution so that formation of the 3 : 1 compound is possible, but too great a pressure results in the formation of the more compact structure, as might be expected, the pressure in this case preventing the formation of the more open structure and thus, in a sense, forcing the carbon dioxide out again. It appears at first surprising that under similar high pressure but with water as solvent the product contains no carbon dioxide, and does not have the compact α-structure. Instead, it has a low density and the structure of the very open double cagework found in the 3 : 1 molecular compounds. Since the effect of pressure cannot well be to produce this open structure which in other conditions appears to require at least a considerable proportion of its cavities filled by small molecules for stability, and since the observed effect of pressure in benzene solution is in fact to produce the compact form, the explanation must be sought in some specific behaviour of water. It has already been pointed out that water appears not to form a compound with quinol, and this has been attributed to the small dimensions of the water molecule which is not retained by the cageworks. Under pressure it will be possible for water molecules to pass freely through the quinol cage structure—it has been mentioned that the distance of a cage oxygen atom from a water molecule which enters through a hydroxyl hexagon is very little greater than that between two oxygen atoms in liquid water In these conditions the external pressure is rendered ineffective since it is transmitted also to the interior of the cages through water which occupies the spaces. The cavities that could otherwise be held responsible for the instability of the open structure are in this case filled even more effectively than by the sulphur dioxide or other molecule. It is not yet known with certainty whether all the water emerges from the structure when the pressure is removed. Benzene or other large solvent molecule cannot penetrate in this way and thus does not obscure the pressure effect.

Phenols and hydrogen bromide. A study of the behaviour of polyhydric phenols and their ethers with regard to the formation of addition compounds with hydrogen bromide has been made by Gomberg and Cone (*Annalen*, **1910**, **376**, 237) with the following results. Orcinol (III) and phloroglucinol (IV) form compounds, HBr,2M, which are presumed to be of the same general character as the 3 : 1 compound with quinol (V) already known to be of the clathrate type. The other molecules (VI)—(XIII) do not form compounds with hydrogen bromide. Those without hydroxyl groups cannot link to form cage structures; those with only one hydroxyl group do not fulfil the requirement for the formation of a large space that they should be capable of attachment at two or more widely separated points. There is no relationship of number or position of the hydroxyl groups that correlates with the formation of compounds by (III), (IV), and (V) and the failure of (VI) and (VII) to give similar compounds. On the other hand, there is a close similarity of shape and size of molecules (III) and (IV) and the possibility of hydrogen-bond linking at two or more points with hydrogen bond directions restricted by the rigid framework of the molecules. The formula 2 molecules : 1HBr, like that

of the 3 : 1 compound of (V), appears to be unrelated to any chemical characteristic such as the number of hydroxyl groups. The formation of compounds by (III) and (IV) is therefore



provisionally explained by supposing that the requirements of the hydrogen-bond linking lead to a cage structure in the crystals with spaces large enough to contain a hydrogen bromide molecule which represents a small volume compared to that of the two molecules with which it is combined.

Amines and aminophenols with sulphur dioxide. Lumière and Seyewitz (*Bull. Soc. chim.*, 1906, **35**, 1204) prepared addition compounds by the action of sulphur dioxide on aqueous suspensions of *p*-aminophenol, *p*-methylaminophenol, or *p*-phenylenediamine. The compositions, based however on determinations of sulphur dioxide content only, correspond approximately to the formulæ $10NH_2{\cdot}C_6H_4{\cdot}OH,H_2SO_3$, $6CH_3{\cdot}NH{\cdot}C_6H_4{\cdot}OH,H_2SO_3$, and $9NH_2{\cdot}C_6H_4{\cdot}NH_2,H_2SO_3$. These compounds do not lose their sulphur dioxide readily, melt (with liberation of sulphur dioxide) at or near the melting points of the parent amine or aminophenol, and have compositions which it is difficult to explain by ordinary constitutional formulæ. All three parent substances bear a close resemblance to quinol, being capable of hydrogen-bond formation through the oxygen or nitrogen atoms in *para*-positions to each other. It seems very probable that they form cage structures which enclose sulphur dioxide and perhaps water. Since the compositions may be variable in ways discussed previously, a more precise determination of the formula would best be obtained from crystal-structure examination. The melting points of these compounds may be those of the respective decomposition products. In this they resemble the compounds of quinol mentioned above, some of which have been shown to decompose into quinol at temperatures below the observed " melting points " which are very close to that of quinol itself.

Choleic acids. The choleic acids in which deoxycholic acid combines with a small proportion of fatty acid, hydrocarbon, or a variety of other substances bear some resemblance to clathrate compounds. It is clear from the so-called co-ordination numbers of deoxycholic acid per fatty acid molecule (Rheinbolt, *Annalen*, 1927, **451**, 256) which have the values 1, 3, 4, 6, or 8, increasing with chain length of the fatty acid, that the amount of material combined with the deoxycholic acid is determined by its volume, for if the formulæ are rewritten for constant amount of deoxycholic acid the numbers of combined fatty acid molecule diminish with increasing chain length. However, since molecules of very different lengths from 2 to 16 carbon atoms may enter into the compounds, the case is not exactly parallel to those discussed above. It is inherently more probable that the second component is here contained in extended channels formed by a structure of deoxycholic acid, rather than in closed cavities of limited dimensions; this is in agreement with available data on the crystal structures (Go and Kratky, *Z. physikal. Chem.*, 1934, *B*, **26**, 439; Giacomello, *Atti R. Accad. Lincei*, 1938, **27**, 101; *Gazzetta*, 1939, **69**, 790).

Decomposition by mechanical means. In the absence of any strong attachment of the enclosed molecules to their surroundings it should be possible to set them free by mechanical breaking of the cage. Crystals of the sulphur dioxide–quinol compound have been kept loosely corked for years and appear to last indefinitely when freely exposed to the air, but on being ground they liberate enough sulphur dioxide to be detected by smell. It is difficult to distinguish this from ordinary inclusions or from effects attributable to local heating, but that a noticeable amount of decomposition could occur is shown as follows.

For simplicity it may be assumed that the large crystals have been crushed to cubes of side a. The original surface is negligible compared to the new surface, and if all surface cages to a depth b are unsealed the volume of decomposed material for each cube is approximately $6a^2b$ when a

is large compared to b. The fraction of decomposed material obtained by dividing this by the volume of the cube is $6b/a$, *i.e.*, it is inversely proportional to the linear dimension of the fragment. Since the crystals are not cubic, the unit cell dimension depends on the direction considered, and a reasonable value for decomposition extending to one unit cell depth only is of the order of 10 A., or 10^{-7} cm. $= b$. If crystals are ground to a size $a = 10^{-3}$ cm., the proportion decomposed is thus 6×10^{-4}, or of the order of 0·1%.

Enclosure in solution and at surfaces. It has been shown (Lepenski, *Kolloid-Z.*, 1943, **105**, 144) from a study of the Plotnikow effect that quinol is strongly polymerised in ethyl-alcoholic or ethereal solution, and the possibility arises that cage polymers may be formed in solutions of this or other substances capable of hydrogen-bond formation. A space may be enclosed by a polyhedron having the molecules as its faces and OH . . . O bonds where the polyhedron faces meet at a corner. For a molecule which is not flat but has the general shape of a saucer with suitably placed hydroxyl groups on the rim it would be sufficient to link two only. Puckered ring systems with projecting hydroxyl groups are suitable. Such a union cannot be expected to occur in the presence of solvent molecules which would have to move away to form the empty space, but if solvent or other solute may be enclosed the complex will be stabilised. Enclosure of this type may explain why insoluble substances such as fats and hydrocarbons may be brought into solution in presence of deoxycholic acid. This molecule has hydroxyl groups that may lead to formation of enclosures somewhat different from those in the crystalline choleic acids. If the enclosures are of some permanence, the effective concentration of hydrocarbon molecules in solution in equilibrium with the solid or liquid hydrocarbon is much less than the total concentration which includes the enclosed material. Solution in this way is analogous to the solution of a normally insoluble salt by formation of a more complex ion.

Quinol and similar hydrogen-bond-forming molecules will attach themselves to surfaces, as is shown by the oriented growth of quinol on suitable crystal surfaces. When this occurs surface cages must be formed, and according to the conditions these could be of a permanent or a transient kind. The resulting proximity of any enclosed molecules may have an influence on reactions between the enclosed materials, the surface and the enclosing cage or between some of them, since it affects the chances of reacting substances being not only in the right places but also in suitable internal phases or states of activation. The restrictions on movement and possible packing positions of the enclosed materials could in some forms of cage lead to a preferential formation of particular isomers, including optical isomers. Loose compounds of this kind may play a part in reactions of biological importance.

Note added in Proof.—Since the prediction of the α-quinol structure was made, *X*-ray results have been obtained which do not agree with those previously reported. The structure therefore requires modification. It is more complex, but the c dimension is unchanged and there is little doubt of the validity of the main conclusion that an essential component is the interlocking group of quinol molecules enclosing a cavity.

The author wishes to express his thanks to the research department of Messrs. I.C.I. Ltd., Billingham Division, who carried out the high-pressure crystallisations.

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16. *Some Catalysed Gas-phase Reactions of Aromatic Hydrocarbons. Part II. The Interaction of Benzene and Ethylene.*

By D. LL. HAMMICK and M. ROBERTS.

Methods of preparing ethylbenzene, suitable for industrial application, have been investigated during a programme of research on the catalytic alkylation of aromatic compounds. It was found that, over catalysts of the dehydrating type at temperatures of 450—500°, benzene could be made to react with ethylene at ordinary pressures to give predominantly monoethylated products. Under favourable conditions in a flow apparatus, yields of about 8% of ethylbenzene were obtained over bauxite.

THE preparation of toluene in useful yield by the gas-phase interaction at atmospheric pressures of benzene and dimethyl ether over solid dehydrating catalysts has been carried out by Given and Hammick (*J.*, 1947, 928). Attempts to form ethylbenzene by an analogous reaction

do not promise to be very successful, because diethyl ether is known to decompose almost quantitatively over dehydrating catalysts to give ethylene and water (cf. Senderens, *Ann. Chim. Phys.*, 1885, **8**, 505). Nevertheless, detectable amounts of ethylbenzene can be obtained from benzene and diethyl ether, and yields would presumably be higher if the water produced did not seriously deactivate the catalyst. This suggests the possibility that ethylene itself might be a more satisfactory compound for catalytic gas-phase ethylation under ordinary pressures.

As is well known, a vast industrial production of ethylbenzene has grown up during the last decade in Germany and U.S.A., and it is clear that the catalysed ethylation of benzene by continuous flow methods *under pressure* using ethylene has been widely exploited (Sachanen and O'Kelly, *Ind. Eng. Chem.*, 1941, **33**, 1540; *Oil and Gas J.*, 1942, **41**, No. 13, p. 14; Pardee and Dodge, *Ind. Eng. Chem.*, 1943, **35**, 273; Schaad, U.S.P. 2,290,211, 1943, for Universal Oil Products Co.; Mattox, *Trans. Amer. Inst. Chem. Eng.*, 1945, **41**, 463).

In the work to be described, however, it has been shown that benzene and ethylene can give reasonable yields of ethylbenzene under flow conditions at ordinary pressures. A number of non-volatile and easily recoverable catalysts of the dehydrating type were tried, including bauxite, aluminium silicate, silica gel, basic aluminium phosphate, activated alumina, and titania gel. A reduced nickel–aluminium silicate gave no ethylbenzene, but small amounts of toluene (cf. Komarewsky, *J. Amer. Chem. Soc.*, 1937, **59**, 2715). Of the other catalysts, bauxite was by far the best; aluminium silicate was also reasonably active. At 450°, under the most favourable conditions, *i.e.*, slow rates of flow of benzene and approximately equimolecular proportions of the reactants, yields of 8·2% of ethylbenzene could be obtained with bauxite (yields are calculated as moles per 100 moles of benzene used). The other catalysts tried gave very small or negligible amounts of alkylated products.

Undesirable by-products were not obtained, and the unchanged reactants were recoverable in very good yield. The effective catalysts are easily handled and, with suitable reactivation, can be used indefinitely.

Experimental.

Flow Apparatus.—The vapourised reactants were passed at measured rates through a pre-heater at 250° into a "Pyrex" tube 93 cm. long enclosed in a box-type electric furnace. Ethylene (about 98% pure) was obtained from a cylinder of the compressed gas, and its rate measured by a calibrated flow-meter. Benzene ("AnalaR") was boiled electrically in a calibrated apparatus which gave rates of distillation dependent only on the current supplied (cf. Adkins, *J. Amer. Chem. Soc.*, 1922, **44**, 2175; Given and Hammick, *loc. cit.*). About 450 g. of catalyst, crushed and screened between 2/8 mesh, were used, and the free space in the furnace tube was approximately 300 c.c. The liquid products were condensed out, and the gaseous products collected for analysis when required.

Catalysts.—The bauxite was obtained from Messrs. Harrington Bros., and the aluminium silicate from Messrs. Peter Spence Ltd. The catalysts were dried thoroughly at 500° for several hours in the furnace before use, and had the compositions shown in Table I.

Table I.

Catalyst.	Loss on ignition, %.	Composition, %. Al_2O_3.	SiO_2.	Fe_2O_3.	TiO_2.	Traces of
Bauxite	22·7	35·6	30·9	6·9	4·3	Cr, Mn, SO_4
Aluminium silicate	7	41—42	48	1	1—2	Cr

The nickel–aluminium silicate was prepared by evaporating 450 g. of the aluminium silicate with a solution of 50 g. of nickel nitrate, drying the product in an air-oven at 200°, and decomposing it in the furnace tube at 400°. The nickel oxide was reduced in hydrogen at 350—400° for several hours, and the nickel–aluminium silicate catalyst finally heated at 500° in an atmosphere of hydrogen before use.

Analysis of Products.—Liquid products were analysed by fractional distillation in a Podbielniak type of still. Sharp separation of benzene and ethylbenzene (less than 0·5 c.c. distilled between the "plateaux") was easily obtained. The composition of gases was determined in a standard Bone and Wheeler apparatus.

Characterisation of Aromatic Products.—The hydrocarbon, b. p. 136°, obtained in an ethylation experiment was confirmed as ethylbenzene by refractive-index determinations with an Abbé refractometer, by quantitative analysis, and by bromination by the method of Friedel and Crafts (*Compt. rend.*, 1885, **101**, 1220) (see Table II).

Table II.

Hydrocarbon.	$n_D^{14.5°}$.	C, %.	H, %.	M. p. of Br_8-derivative.	Mixed m. p. + authentic specimen.	Br, %, in Br_8-derivative.
B. p. 136°	1·4976	90·0	9·2	141—142° (*ex* EtOH)	140—143°	79·8
Authentic ethylbenzene.....	1·4980	90·6	9·4	141°	—	80·0

The suspected toluene obtained over nickel–aluminium silicate was converted into a pentabromo-derivative with bromine and aluminium chloride. This on recrystallisation from toluene melted at 277—279°. Pentabromotoluene prepared from authentic toluene melted at 279—281°, and a mixed m. p. with the bromo-derivative showed no depression.

Results.—(a) *Aluminium silicate.* A series of experiments with this catalyst showed that fair yields of ethylbenzene could be obtained by using slow rates of benzene flow. In the two final runs (Table III*a*), benzene and ethylene were passed over the catalyst in approximately equimolecular proportion. Deactivation of the catalyst is clearly shown by runs 1 and 2 carried out consecutively under identical conditions. For this reason, oxygen was passed over the aluminium silicate at 500° before each subsequent experiment (see below in connection with bauxite). The products were pale yellow, slightly cloudy liquids. Higher homologues of ethylbenzene were not formed in measurable amount.

TABLE III.

Expt.	Temp.	Rate C_2H_4, l./hr.	Rate C_6H_6, g./hr.	Time of expt. (hrs.).	Yield of EtPh, c.c.	Yield of EtPh, % (on C_6H_6).
			(*a*) *Aluminium silicate.*			
1	450°	1·0	21·7	3·0	1·4	1·4
2	450	1·0	21·7	3·0	0·8	0·8
3	450	1·0	21·7	3·0	1·3	1·3
4	500	2·3	17·0	4·0	2·6	2·5
5	500	3·6	17·0	4·0	3·0	2·8
6	450	3·6	13·5	3·75	3·1	4·0
7	500	3·6	13·5	3·75	3·1	4·0
			(*b*) *Bauxite.*			
8	450	3·6	17·0	3·5	5·5	6·0
9	450	5·0	17·0	3·5	5·6	6·1
10	450	5·0	13·5	4·0	6·9	8·2

(b) *Bauxite.* Similar results were obtained with bauxite (for composition, see above), but percentage yields were approximately double. Again, reactivation of the used catalyst in oxygen at 500° was carried out before each experiment. Products were slightly cloudy, pale yellow liquids. Typical figures are given in Table III*b*.

(c) *Nickel–aluminium silicate.* This catalyst gave no yield of ethylbenzene, but instead a small fraction boiling at 110°. Toluene was shown here to be the only alkylated product (Table IV).

TABLE IV.

Expt.	Temp.	Rate C_2H_4, l./hr.	Rate C_6H_6, g./hr.	Time of expt. (hrs.).	Yield of MePh, c.c.	Yield of EtPh, c.c.
11	450°	3·6	17·0	3·7	1·4	0
12	450	3·6	17·0	3·7	1·2	0

(d) *Recovery of the reactants.* Benzene and other aromatic compounds are unchanged in the presence of metallic oxides below at least 600° (cf. Beilstein, "Handbuch," Bd. V, 185). The existing data on ethylene are contradictory (cf. Egloff, "Reactions of Pure Hydrocarbons," 1937, p. 260), but decomposition should be slight below 500°. This was confirmed for aluminium silicate and bauxite, over which ethylene was passed and the gaseous products collected and analysed (Table V). Over nickel–aluminium silicate, decomposition was considerable, with formation of much methane and hydrogen.

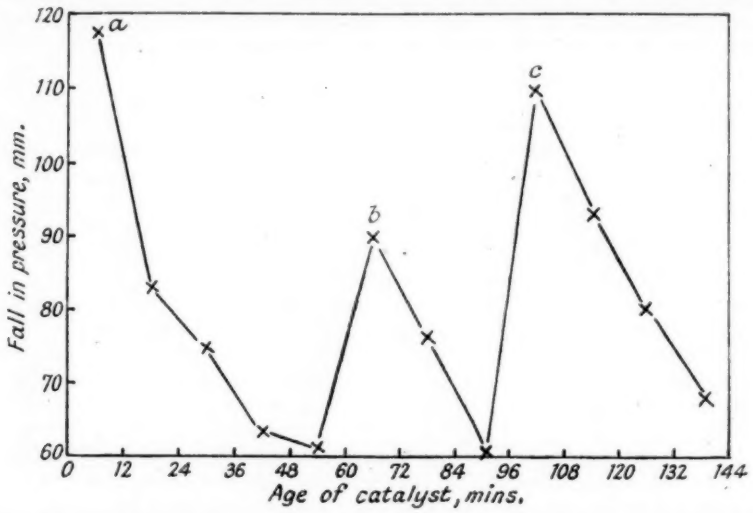
TABLE V.

Conditions.	Higher olefins.	Products, %. CO_2.	C_2H_2.	C_2H_4.	H_2.	O_2.	CO.	Paraffins.	Residue, N_2, etc.
C_2H_4 at 3·6 l./hr. over Al silicate at 500°	1·2	1·1	—	84·9	—	1·1	—	—	11·7
C_2H_4 at 3 l./hr. over bauxite at 450°	1·2	1·2	—	91·5	1·5	0·6	—	—	4·0
C_2H_4 at 3·6 l./hr. over Ni–Al silicate at 450°	1·1	1·3	0·8	62·7	14·3	1·0	1·1	14·9 (n = 1·6)	2·8
Original C_2H_4 from cylinder...	0·7	—	—	97·5	—	—	—	—	1·8

(e) *Deactivation and reactivation of bauxite.* Bauxite and other catalysts used in the benzene–ethylene reaction were found to undergo considerable deactivation during the course of an ethylation experiment (cf. runs 1 and 2, Table III). Investigations in an apparatus of the type used for studying the kinetics of gaseous reactions showed this to be caused by deposition of carbon (presumably from the decomposition $C_2H_4 \longrightarrow 2C + 2H_2$). Complete reactivation could be brought about by passing a stream of oxygen over the catalyst at 500°.

A series of experiments with approximately 150 mm. of benzene and 280 mm. of ethylene were carried out over bauxite at 448°. The figure shows the fall in pressure during an arbitrary period of 10 minutes plotted against the total life of the catalyst. At each point on the graph, the reaction tube was evacuated, the reactants admitted, and the fall in pressure in 10 minutes observed. The total times of each experi-

ment, about 12 minutes, were added together to give the age of the catalyst. The decomposition of ethylene alone (also involving a decrease of pressure) was small compared with the reaction between ethylene and benzene, so the fall in pressure observed was a rough measure of the rate of ethylation.



Point *a* refers to fresh bauxite; point *b* was obtained after air had been admitted to the catalyst at 500°, and *c* after oxygen had been kept in contact with it for a few hours at 500°.

The residual gas left after passing oxygen over the deactivated bauxite at 500° was proved to contain a high proportion of carbon dioxide.

A grant from the D.S.I.R. in support of the above work is gratefully acknowledged by one of us (M. R.).

DYSON PERRINS LABORATORY, OXFORD. [*Received, February 14th*, 1947.]

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17. *The System Ammonia–Sulphur Dioxide–Water at 25°.*

By L. M. HILL.

A partial study has been made of the solid–liquid equilibria in the system ammonia–sulphur dioxide–water at 25°. The work has been confined to the solubility curve for hydrated ammonium sulphite $(NH_4)_2SO_3,H_2O$ at pressures not exceeding one atmosphere. The practical limits for this pressure restriction were found to be solutions containing 23% NH_3, 6% SO_2 and 16% NH_3, 50% SO_2. The monohydrate dissolves congruently and can exist with solutions containing excess of either NH_3 or SO_2. A strong tendency towards supersaturation was encountered.

THE system ammonia–sulphur dioxide–water forms an interesting study since the first two components are gaseous at room temperatures and pressure. In this respect it resembles the system ammonia–carbon dioxide–water which has already been partly described by different workers.

The most extensive published study of the system under consideration is contained in four papers by Terres and Hahn [*Gas- u. Wasserfach*, **1927**, **70**, (*a*) 309—312, (*b*) 339—342, (*c*) 363—367, (*d*) 389—395]. The solubility results are mainly recorded in (*c*), though (*b*) and (*d*) contain relevant matter. Consideration of the system was limited to solutions which have the normal sulphite monohydrate and anhydrous hydrogen sulphite as their solid phase. Isotherms within this range were reported at 0°, 20°, 30°, 40°, 50°, and 60°.

Discontinuities in the monohydrate curve exist in each of the above-mentioned isotherms, and become less evident at the higher temperatures. These irregularities could not be explained on the basis of changes in the chemical composition of the solid phase, and structural changes in the molecule were suggested. Terres and Hahn also included some vapour-pressure measurements in their work.

Apart from the above-mentioned study, no other workers seem to have investigated the ternary system with its variable ammonia and sulphur dioxide concentrations, but there are

records of the solubilities of the different sulphites in water. These isolated binary solutions give single points on ternary curves. Included in this category there are results at 25° by Ishikawa with Murooka and with Hagisawa (Seidell, " The Solubility of Inorganic and Metal Organic Salts ", 1940, Vol. 1, 1120, 1121). Other results at 25° are by Hunt (*J. Amer. Chem. Soc.*, 1932, **54**, 3511) and by Terres and Overdick (*Gas- u. Wasserfach*, 1928, **71**, 106) and 60° and 85° points are to be found in the work of Silbermann and Ivanov (*J. Appl. Chem. U.S.S.R.*, 1941, **14**, Nos. 7—8, 941).

Experimental.

A full examination of this system would have involved the determination of the composition and pressure of the vapour phases which contained all the components. The work was, however, restricted to the equilibrium conditions between solids and solutions whose total vapour pressure did not exceed one atmosphere.

The solubility mixtures were prepared from freshly distilled water, reagent ammonia solution (*d* 0·88), gaseous ammonia, where required, and gaseous sulphur dioxide. Each mixture was placed in an 8-oz. bottle fitted with a glass stirrer whose bearing was sealed by a shallow mercury lute. Before the mixture was stirred in a thermostatically controlled water-bath, the air in the upper part of the bottle was displaced by coal-gas in order to reduce to a minimum the oxidation of the sulphite. A little stannous chloride solution was also used in a few instances to inhibit oxidation, but as the results showed that it failed to achieve its object the addition was discontinued. As the results in the table show, a small and variable amount of sulphate was present in each equilibrium solution in spite of efforts to prevent oxidation.

System NH_3–SO_2–H_2O *at* 25°. Solid phase : $2NH_3,SO_2,2H_2O$.

	Solution. G. per 100 g.			Moist solid. G. per 100 g.		
$d_{15°}^{25°}$.	NH_3.	SO_2.	SO_3.	NH_3.	SO_2.	SO_3.
0·964	23·8	6·5	0·2	24·6	34·8	Nil
1·007	19·9	9·3	—	23·7	40·5	—
1·061	17·4	13·5	Nil	22·4	36·6	Nil
1·101	16·1	15·9	0·3	—	—	—
1·109	15·8	16·4	0·1	—	—	—
—	13·8	19·0	Nil	18·5	30·9	Nil
1·150	13·8	19·2	0·1	—	—	—
—	11·9	20·7	0·7	20·7	38·3	Nil
—	12·1	21·0	—	—	—	—

	Solution. G. per 100 g.			Moist solid. G. per 100 g.		
$d_{15°}^{25°}$.	NH_3.	SO_2.	SO_3.	NH_3.	SO_2.	SO_3.
1·201	11·5	22·0	0·3	—	—	—
1·234	11·8	27·3	0·2	—	—	—
1·278	12·4	33·3	0·3	17·1	38·6	0·2
1·342	13·4	41·4	0·8	19·8	44·6	0·9
1·358	13·8	43·2	0·2	20·8	45·7	1·3
1·371	14·1	44·9	0·4	19·6	46·4	0·5
1·411	14·8	49·2	0·5	19·6	48·6	0·5

A strong tendency for the initial mixtures to remain as clear supersaturated solutions was encountered in many cases, and this was dealt with by " seeding " with a few crystals of hydrated sulphite as soon as some of this had been prepared.

After the solubility mixtures had been stirred long enough to establish equilibrium—tests demonstrated that an overnight period of 17 hours was generally sufficient for this—stirring was stopped in order to allow the solid phase to settle. The clear liquor for analysis was then sampled in a dry pipette and transferred rapidly to a stoppered weighing bottle. In most cases a sample of filtered moist solid phase " residue " was taken and also analysed.

The samples of solution and moist solid were transferred by water to measuring flasks and aliquot proportions were analysed by the following methods :

(1) Sulphite by titration with N/10-iodine solution.

(2) Total sulphur (sulphite + sulphate) determined gravimetrically as barium sulphate after the sulphite had been oxidised to sulphate by bromine in hydrochloric acid solution.

(3) Alkalinity. Titration with N-sulphuric acid, methyl-orange being the indicator (the hydrogen sulphite is neutral to this indicator).

(4) Ammonia. Two methods were employed to varying extents. (*a*) Direct method in which the solution was boiled with sodium hydroxide and the liberated ammonia collected in N-sulphuric acid. (*b*) Indirect method in which ammonia was calculated from determinations (1), (2), and (3)—in equivalents, NH_3 = Alkalinity + ½ sulphite iodine titre + sulphate. The agreement between 4*a* and 4*b* was reasonably good.

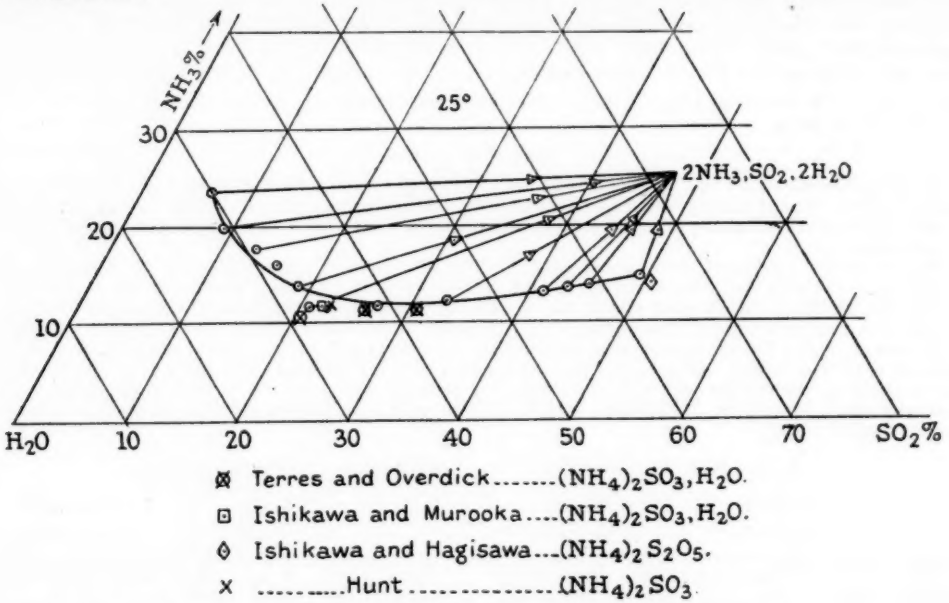
It was found that if further oxidation were to be avoided, the sulphite determination (1) had to be carried out as soon as possible after the sample was taken from the solubility bottle.

The composition of solutions and the corresponding residues are given in the table and plotted in the figure. The solid phase deduced graphically by plotting solution and moist solid compositions is in each case ammonium sulphite monohydrate ($2NH_3,SO_2,2H_2O$) as reported by Isikawa and Murooka for the binary system. The solubility points exhibit some irregularities and these are probably due in varying degrees to the characteristics of the system which have already been mentioned, *i.e.*, volatility of the components, difficulty of preventing oxidation, and supersaturation with respect to the solid phase.

It is possible that solutions with high sulphur dioxide concentrations may lie on a metastable extension of the monohydrate curve. This possibility is supported by the results of Terres and Hahn who, though not working at 25°, obtained at 20° and 40° two solid-phase points each containing about 44% of SO_2.

The shape of the 25° isotherm for solutions containing less than 19% of SO_2 is at variance with the isotherms of Terres and Hahn, who suggest irregular, looped curves with a SO_2 minimum of 16% in their

work at 20°. In the absence of further evidence no opinion can be expressed on the cause of this disagreement.



The author wishes to acknowledge the help of Mr. W. Edge with this investigation.

IMPERIAL CHEMICAL INDUSTRIES RESEARCH DEPARTMENT,
ALKALI DIVISION, NORTHWICH, CHESHIRE. [*Received, February 25th*, 1947.]

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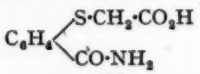
18. *Some* 1 : 3-*Oxazine Derivatives of Thionaphthen.*

By (the late) ERNEST W. MCCLELLAND and DOUGLAS W. STAMMERS.

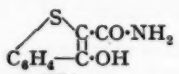
2-Cyanophenylthioacetic acid (IV) condenses with acetic anhydride and potassium acetate, the principal product being 3-acetamido-2-carboxythionaphthen (VI), but yellow by-products (XII) and (XVII) are also formed which are metoxazine derivatives of complexity varying with the conditions of the reaction. Their structures are discussed, and it is also shown that the acetamidocarboxythionaphthen is converted directly by hot acetic anhydride into a thionaphtheno-1 : 3-oxazine (VII) which reacts with ammonia to give the corresponding thionaphthenopyrimidine (VIII).

IN the course of a study of the formation of thionaphthens by condensation of 2-substituted phenylthioacetic acids with acetic anhydride and potassium acetate several thionaphtheno-1 : 3-oxazines have been encountered.

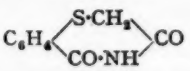
It has been shown (McClelland, Rose, and Stammers, following paper) that 2-carbamylphenylthioacetic acid (I) is converted by acetic anhydride and potassium acetate into the carbamylthionaphthen (II) and that the imide (III) is an intermediate in the process. If, in the



(I.)

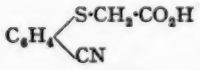


(II.)

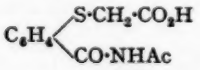


(III.)

similar condensation with the 2-cyano-acid (IV), the first step was an internal self-addition the same imide would result and the carbamidothionaphthen would be the final product.



(IV.)



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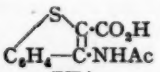
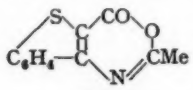


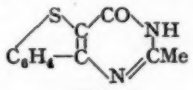
(VI.)

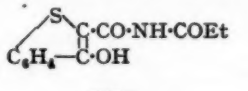
Alternatively, however, addition of acetic acid to the cyano-group might occur to give the 2-acetylcarbamyl acid (V) and this would undergo internal condensation to produce 3-acetamido-

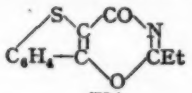
2-carboxythionaphthen (VI). The condensation proceeded, in fact, according to the second of these schemes and the acetamidocarboxythionaphthen was the principal product, but it was accompanied, according to the conditions used, by two yellow *by-products*, A and B, which are discussed below.

The formation of a 1 : 3-oxazine ring was to be expected from substances containing the grouping of (VI), analogous cases being the production of 1 : 3-oxazines from *N*-benzoylanthranilic acid (Shroeter, *Ber.*, 1920, **53**, 230) and α-benzamidocinnamic acid (Erlenmeyer, *Annalen*, 1893, **275**, 1), and experiment showed that this acetamidocarboxythionaphthen is converted by hot acetic anhydride into 6-*keto*-2-*methylthionaphtheno*(3′ : 2′ : 4 : 5)-1 : 3-*oxazine* (VII), which reacted readily with ammonia to give the corresponding *thionaphthenopyrimidine* (VIII) (compare the formation of *iso*carbostyril from *iso*coumarin, Bamberger and Frew, *Ber.*,


(VII.)


(VIII.)

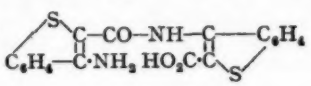

(IX.)

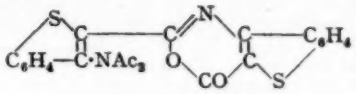

(X.)

1894, **27**, 208; Gabriel and Neumann, *Ber.*, 1892, **25**, 3563). 3-Hydroxy-2-propionylcarbamylthionaphthen (IX) was similarly converted by hot propionic or acetic anhydride into 4-*keto*-2-*ethylthionaphtheno*(2′ : 3′ : 5 : 6)-1 : 3-*oxazine* (X).

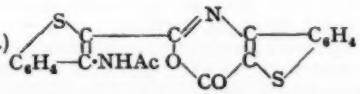
Of the yellow by-products, referred to above, B was obtained when the reaction was conducted at 140—145°. It was of high melting point, was insoluble in alkali, and had a composition which may be expressed in the form (cyano-acid + $CO{\cdot}CH_2$ − $H_2O)_x$, but it was too sparingly soluble in organic solvents or molten camphor for the determination of molecular weight. It was hydrolysed by alcoholic alkali to give sodium acetate and a *substance* C of the composition (cyano-acid − $H_2O)_x$. C was soluble in aqueous bicarbonate, and hot acetic anhydride reconverted it into B. If it is assumed, therefore, that $x = 2$, the substance C might be the amide of structure (XI) and B might be the *N*-diacetyl derivative of a thionaphtheno-1 : 3-oxazine (XII) or the diacetyl derivative of a cyclic diamide such as (XIII). Of these two, structure (XII) requires that the two acetyl groups should differ in ease of hydrolysis.

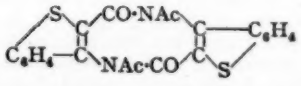
(XI.) (C.)




(XII.) (B.)

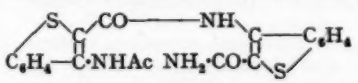
(XII*a*.) (D.)

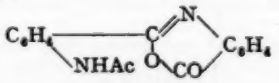


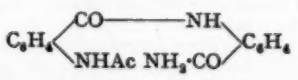

(XIII.)

It was found, in fact, that B readily lost one acetyl group on boiling with 90% acetic acid, yielding a *compound* D which was reconverted into B by acetic anhydride and hydrolysed by alkali to C; B therefore has structure (XII) and D the structure (XII*a*) with NHAc in place of NAc_2. The conclusion was further confirmed by the conversion of D by propionic anhydride into the corresponding N-*acetyl*-N′-*propionyl* compound and of C in a similar manner into its *mono*- and *di*-N-*propionyl* derivatives analogous to D and B respectively.

When B was subjected to the action of ammonia in alcoholic solution no pyrimidine was isolated, but instead 3-*acetamido*-2-(2′-*carbamyl*-3′-*thionaphthenyl*)*carbamylthionaphthen* (XIV) resulted, the metoxazine ring having been opened [compare the action of ammonia on the acetamidophenylbenz-1 : 3-oxazine (XV) to give acetylanthranoylanthranilic acid amide (XVI); Mohr and Kohler, *Ber.*, 1907, **40**, 997].


(XIV.)

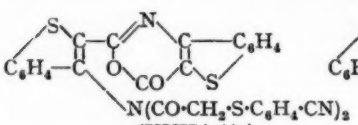

(XV.)


(XVI.)

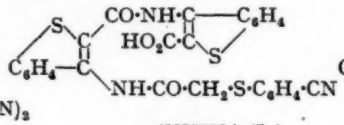
When the condensation with cyanophenylthioacetic acid was carried out at a lower temperature (100°), another by-product A was produced which was highly insoluble and of the composition (cyano-acid − $H_2O)_m$. It was acted upon by hot acetic anhydride to produce B (XII) together with some of the acetamidocarboxythionaphthen. Vigorous hydrolysis of A yielded C (XI) without the formation of any sodium acetate. Hydrolysis under milder conditions gave 3-amino-2-carboxythionaphthen and a new highly insoluble *substance* L of a

composition represented by (3 cyano-acid — $2H_2O$). L, boiled with either acetic or propionic anhydride, was converted into a *substance* M with the composition (cyano-acid — $H_2O)_n$ which was reconverted into L by cold alcoholic alkali; M thus had the same empirical composition as A but was quite distinct from it. Friedländer and Laske's observation (*Annalen*, 1907, **351**, 416) that the 2-cyanophenylthioacetic acid is itself converted on standing with cold alcoholic alkali into 3-amino-2-carboxythionaphthen was confirmed.

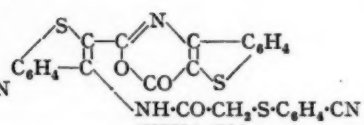
Bearing in mind that the presence of the cyano-acid appears to be a condition of the formation of the yellow by-products, the facts above summarised lead to the supposition that $m = 4$ and $n = 3$ in the above expressions and that A has the structure (XVII). Its conversion into B (XII) by acetic anhydride is then a simple displacement of cyanophenylthioacetyl radicals by acetyl radicals. L will therefore be the substance (XVIII) closely related to (XIV) and M must have the 1 : 3-oxazine structure (XIX) analogous to D.



(XVII.) (A.)



(XVIII.) (L.)



(XIX.) (M.)

Experimental.

Condensation of 2-Cyanophenylthioacetic Acid with Acetic Anhydride and Potassium Acetate.—(1) 2-Cyanophenylthioacetic acid (10 g.; cf. Friedländer and Laske, *loc. cit.*, p. 413; D.R.-P. 184,496) was heated for ½ hour at 140—145° with acetic anhydride (30 c.c.) and potassium acetate (7·5 g.). The solid deposited on cooling was washed with acetic anhydride and with water and heated for ½ hour at 100° with acetic acid (100 c.c.; 80%). The solid product was separated when cold and extracted with aqueous sodium hydroxide (30 c.c.; 2N) at 60° for ½ hour. The alkaline solution on acidification yielded 3-acetamido-2-carboxythionaphthen, m. p. 230° (yield, 6·4 g.).

The residue insoluble in alkali (compound B) formed yellow prisms, m. p. 259°, from acetic anhydride (yield 0·9 g.). This was 3-*diacetylamino*-2-6′-*ketothionaphtheno*(3″ : 2″ : 4′ : 5′)-1 : 3-*oxazinyl*-2′-*thionaphthen* (XII) (Found: C, 60·7; H, 3·4; S, 14·9. $C_{22}H_{14}O_4N_2S_2$ requires C, 60·8; H, 3·2; S, 14·7%). It gave no coloration with ferric chloride or alkaline ferricyanide.

When heated in 90% acetic acid this substance suffered partial hydrolysis, and yellow needles of the *monoacetyl* compound D (XII*a*), m. p. 312°, separated, which were washed with hot alcohol and dried at 100° (Found: C, 61·4; H, 3·3; S, 16·2. $C_{20}H_{12}O_3N_2S_2$ requires C, 61·2; H, 3·1; S, 16·3%). This substance is insoluble in alkali and gives no colour with ferric chloride or alkaline ferricyanide. It is reconverted into compound B by heating with acetic anhydride, and with propionic anhydride yields the corresponding N-*acetyl*-N′-*propionyl* derivative, crystallising from propionic anhydride in yellow plates, m. p. 230° (Found: C, 61·7; H, 3·9. $C_{23}H_{16}O_4N_2S_2$ requires C, 61·6; H, 3·6%).

When B (XII) was heated in boiling alcohol for 1½ hours with a stream of ammonia passing, a small amount of compound D (XII*a*) was deposited early in the operation and was removed. The final solution on evaporation to dryness yielded 3-*acetamido*-2-(2′-*carbamyl*-3′-*thionaphthenyl*)*carbamylthionaphthen* (XIV) as a pale yellow microcrystalline powder of m. p. 284—286° (Found: C, 58·9; H, 3·9; N, 10·2. $C_{20}H_{15}O_3N_3S_2$ requires C, 58·7; H, 3·7; N, 10·3%).

When either D (XII*a*) or B (XII) was hydrolysed by alcoholic sodium hydroxide (10 parts; 5%) and the solution acidified at 70°, a solid was obtained which crystallised from glacial acetic acid in yellow needles, m. p. 246°, and was 3-*amino*-2-(2′-*carboxy*-3′-*thionaphthenyl*)*carbamylthionaphthen*, compound C (XI) (Found: C, 58·7; H, 3·5; S, 17·4. $C_{18}H_{12}O_3N_2S_2$ requires C, 58·7; H, 3·3; S, 17·4%). The aqueous mother-liquor from this hydrolysis contained sodium acetate and on distillation in steam yielded some 3-hydroxythionaphthen. C (XI) dissolved in aqueous sodium hydrogen carbonate with evolution of carbon dioxide. It gave no colouration with ferric chloride or alkaline ferricyanide. Heated with acetic anhydride it was reconverted into B (XII). Heated with propionic anhydride at 100° for ½ hour it yielded the N-*propionyl* derivative as yellow needles, m. p. 296°, from propionic anhydride (Found: C, 62·2; H, 3·2. $C_{21}H_{14}O_3N_2S_2$ requires C, 62·1; H, 3·4%). When heating was continued for a further ½ hour until all solid dissolved, the NN′-*dipropionyl* derivative separated on cooling in yellow prisms, m. p. 246° (Found: C, 62·2; H, 4·1. $C_{24}H_{18}O_4N_2S_2$ requires C, 62·3; H, 3·9%). Boiled for 1 hour with 90% propionic acid, this compound suffered partial hydrolysis to the preceding *N*-propionyl derivative.

(2) When 2-cyanophenylthioacetic acid was heated with acetic anhydride and potassium acetate at 100° for 40 minutes and the products were treated as before, the alkali-insoluble product was again 3-acetamido-2-carboxythionaphthen (yield 5 g.), but the residue was a bright yellow solid separating as a microcrystalline powder, m. p. 277—279°, from nitrobenzene (yield 0·8 g.). This compound A (XVII) was 3-(*bis*-o-*cyanophenylthioacetyl*)*amino*-2-6′-*ketothionaphtheno*(2″ : 3″ : 5′ : 4′)-1 : 3-*oxazinyl*-2′-*thionaphthen* (Found: C, 61·5; H, 2·8; N, 7·9. $C_{34}H_{20}O_4N_4S_4$ requires C, 61·7; H, 2·9; N, 8·0%). It was sparingly soluble in all organic solvents and unaffected by boiling in 80% acetic acid for 6 hours. When it was heated at 145° for 3 hours with acetic anhydride it yielded 3-acetamido-2-carboxythionaphthen and compound B. On hydrolysis with alcoholic sodium hydroxide (15%) for 4 hours it gave the yellow compound C (XI) of m. p. 246° and the mother-liquor was found not to contain sodium acetate.

A (XVII) was partly hydrolysed by standing for 24 hours with 5% aqueous alcoholic sodium hydroxide with occasional shaking. The solution was evaporated, the residue dissolved in water, and the solution

acidified at 70° with acetic acid. The precipitate was collected, washed, and dried in a vacuum and extracted with boiling light petroleum, evaporation of which yielded a trace of 3-amino-2-carboxythionaphthen. The residue was further purified by boiling with acetic acid and crystallised from nitrobenzene as a pale yellow microcrystalline powder, m. p. 260°. This was L (XVIII), *3-o-cyanophenylthioacetamido-2-(2′-carboxy-3′-thionaphthenylcarbamyl)thionaphthen* (Found: C, 59·6; H, 3·4. $C_{27}H_{17}O_4N_3S_3$ requires C, 59·7; H, 3·1%). It was sparingly soluble in organic solvents but soluble in aqueous alkali. It gave no colouration with ferric chloride or alkaline ferricyanide. Heated for a few minutes with boiling acetic or propionic anhydride it yielded the alkali-insoluble M (XIX), *3-o-cyanophenylthioacetamido-2-6′-ketothionaphtheno(2″ : 3″ : 5 : 4)-1 : 3-oxazinyl-2′-thionaphthen* as orange needles which could not be recrystallised. It was best obtained pure by preparing it from purified material and finally boiling the product successively with acetic acid and absolute alcohol (Found: C, 61·5; H, 3·2; S, 18·3. $C_{27}H_{15}O_3N_3S_3$ requires C, 61·7; H, 2·9; S, 18·0%). It was reconverted into its parent compound by standing in alcoholic alkali followed by acidification.

Metoxazines from Substituted Thionaphthens.—3-Acetamido-2-carboxythionaphthen was heated with acetic anhydride (4 parts) at 145° for ½ hour. The mixture yielded, on cooling, *6-keto-2-methylthionaphtheno(3′ : 2′ : 4 : 5)-1 : 3-oxazine* (VII) as colourless needles, m. p. 179° (Found: C, 60·7; H, 3·4; S, 14·8. $C_{11}H_7O_2NS$ requires C, 60·8; H, 3·2; S, 14·7%). It was insoluble in alkali, gave a bright yellow colour with ferric chloride, and was hydrolysed to the parent substance by boiling for 20 minutes with 80% acetic acid. Heated at 40° for 20 minutes with alcoholic ammonia [30 c.c. of ethanol and 80 c.c. of ammonia (*d* 0·88) per g.] and then for a further 1 hour at 60°, it furnished *4-keto-2-methyl-3 : 4-dihydrothionaphtheno(2′ : 3′ : 5 : 6)pyrimidine* (VIII) which crystallised in colourless needles, m. p. 340—345° (decomp.), from acetic acid (Found: C, 60·9; H, 3·9; N, 13·1. $C_{11}H_9ON_2S$ requires C, 61·1; H, 3·7; N, 13·0%). This substance dissolved in dilute alkali and was reprecipitated unchanged on acidification. It gave no colour with ferric chloride or alkaline ferricyanide.

3-Hydroxy-2-propionylcarbamylthionaphthen (McClelland, Rose, and Stammers, *loc. cit.*), heated at 130° for ½ hour with propionic anhydride or acetic anhydride, gave *4-keto-2-ethylthionaphtheno-(2′ : 3′ : 5 : 6)-1 : 3-oxazine* (X) as colourless plates of m. p. 209° (Found: C, 62·2; H, 4·0. $C_{12}H_9O_2NS$ requires C, 62·3; H, 3·9%). It was reconverted into the parent substance by boiling with dilute acetic acid. It was insoluble in alkali, and gave no immediate colour with ferric chloride but a green colouration on warming.

The corresponding 3-hydroxy-2-acetylcarbamylthionaphthen under similar conditions yielded only the acetyl derivative of m. p. 130°.

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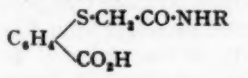
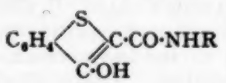
19. *The Formation of Thionaphthens from Derivatives of Phenylthioacetic Acid.*

By (the late) ERNEST W. MCCLELLAND, MAURICE J. ROSE, and DOUGLAS W. STAMMERS.

Condensation of either 2-carboxyphenylthioacetamide (I) or 2-carbamylphenylthioacetic acid (III; R = H) with potassium acetate and acetic anhydride yields the same 3-hydroxy-2-carbamylthionaphthen (II; R = H), the latter change involving a migration of the amino-group. It is shown that this transformation occurs through the cyclic *imide* (IV) which has been isolated and shown to yield the same products. A number of analogous compounds with alkyl or aryl groups substituted in the amino-group have been prepared and shown to behave in a similar manner. The mechanism of this reaction and that of the closely related condensation with benz*iso*thiazolones under similar conditions are discussed in detail.

2-CARBOXYPHENYLTHIOACETAMIDE (I; R = H) reacts normally with potassium acetate and acetic anhydride to give 3-hydroxy-2-carbamylthionaphthen (II; R = H) (compare McClelland, Rose, and Bartlett, *J.*, 1940, 323) but the isomeric amide (III; R = H) also gives this carbamylthionaphthen under similar conditions. The formation of carbamylthionaphthens equally from such isomeric amides appears to be general, for it has now been found that the *N*-substituted amides (I; R = Ph or CH_2Ph) and (III; R = Me, Et, CH_2Ph, or Ph) give the corresponding *N*-substituted carbamylthionaphthens. The conversion of amides of the type (I) into carbamylthionaphthens involves a simple dehydration but the conversion of the isomeric amides (III) involves a migration of the amino-group from one carbonyl group to the other. It seemed probable that this change occurs through the intermediate formation of a seven-membered ring compound (IV) produced by loss of water, and dehydration of the amide (III) under suitable conditions gave a substance which proved to be in fact an *imide* of the


(I.)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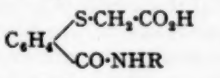
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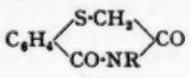
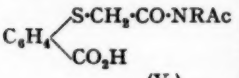

(IV.)

structure (IV; R = H). Thus, hydrolysis of the imide gives *o*-carboxyphenylthioacetic acid; it forms a potassium salt, which on treatment with alkyl halides gives the N-*alkylimides*

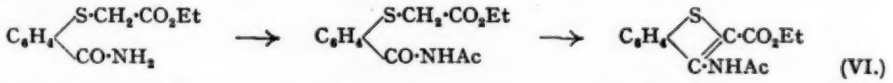
(IV; R = Me or Et). The N-*arylimides* (IV; R = CH_2Ph or Ph) on the other hand were obtained by dehydration of the corresponding amides (III; R = CH_2Ph, Ph).

The observation that the imide and its *N*-derivatives, when heated with potassium acetate and acetic anhydride, gave the corresponding hydroxycarbamylthionaphthens, supports the view that such seven-membered ring compounds are intermediates in the transformation observed. The change from the cyclic intermediate to the hydroxycarbamylthionaphthen may be conceived either as a direct change due to valency rearrangement with migration of one hydrogen atom, or through some intermediate compound produced by ring opening, such as (V).



(V.)

The formation of seven-membered ring compounds requires a free carboxyl group in the amide since the corresponding ester (ester of III) reacts normally with potassium acetate and acetic anhydride to give the aminothionapthen derivative (VI) and not a carbamylthionaphthen. It seems probable that the first stage in this reaction is acetylation of the amino-group, which by decreasing the basic properties of the nitrogen atom must enhance the reactivity of the carbonyl group. This will favour the internal condensation to the aminothionaphthen thus:

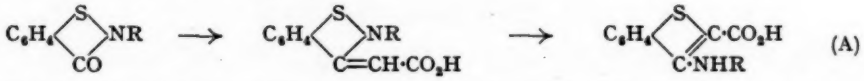


(VI.)

In addition to the hydroxycarbamylthionaphthen, 3-acetoxythionaphthen and 3-hydroxy-2-acetylthionaphthen were usually obtained in the reactions of the amides (I) and (III) with potassium acetate and acetic anhydride, referred to in the first paragraph above.

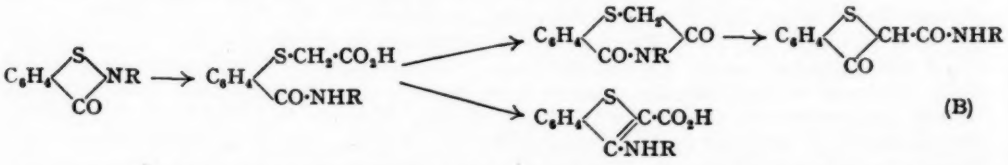
It has been shown (McClelland, *J.*, 1929, 1588; McClelland and D'Silva, *J.*, 1931, 2972) that benz*iso*thiazolones react with potassium acetate and acetic anhydride to give the hydroxyacetylthionaphthens and carbamylthionaphthens, and in the case of *N*-acylbenz*iso*thiazolones, aminothionaphthens. The latter have not been isolated where the *N*-substituent of the benz*iso*thiazolone is an alkyl or aryl group.

It was suggested (Bartlett and McClelland, *J.*, 1934, 818) that thionaphthens were formed from benz*iso*thiazolones by the following steps:



(A)

but this does not explain the production of carbamylthionaphthens which had not at that time been detected as products. The similarity in the products of the reaction of amides of type (III) and of benz*iso*thiazolones with potassium acetate and acetic anhydride suggests that the amide is an intermediate in the reaction of a benz*iso*thiazolone. It seems probable, therefore, that the first stage in the reaction of a benz*iso*thiazolone with potassium acetate and acetic anhydride is ring fission to give amides of this type, which react in the manner described to give the seven-membered ring and hence hydroxycarbamylthionaphthens thus:



(B)

The formation of acylamidothionaphthens when *N*-acylbenz*iso*thiazolones react with potassium acetate and acetic anhydride may be due to the reaction proceeding in part by mechanism (A), or alternatively that the *N*-acylamide produced by ring fission of the benz*iso*thiazolone yields the aminothionaphthen by internal condensation. The acetyl group of the amide should enhance the reactivity of the carbonyl group in either (A) or (B) and thus promote this process. The absence of the aminothionaphthen type of compound in the reaction products from *N*-aryl- or -alkyl-benz*iso*thiazolones can be attributed to the lower reactivity of the carbonyl group preventing the formation of the aminothionaphthen. The *N*-alkyl- or -aryl-amides therefore tend to give the seven-membered ring intermediate and yield hydroxycarbamylthionaphthens to the exclusion of aminothionaphthens.

It has been previously shown that hydroxycarbamylthionaphthen itself reacts with

potassium acetate and acetic anhydride to give 3-hydroxy-2-acetylthionaphthen and 3-acetoxythionaphthen.

The suggestion also made previously (McClelland and Bartlett, *loc. cit.*), that direct carbon-acetylation might be involved in the formation of 3-hydroxy-2-acetylthionaphthen, has now been subjected to a rigorous experimental test. It was found that 3-hydroxy-2-propionylcarbamylthionaphthen, heated with propionic anhydride and sodium propionate, yielded in the same way a mixture of 3-hydroxy-2-propionylthionaphthen and 3-propoxythionaphthen, yet carefully purified 3-propoxythionaphthen heated under similar conditions did not give any of the 2-propionyl derivative. The idea that direct carbon-acylation takes place is therefore negatived.

Hence all the products so far detected in the reaction of various benz*iso*thiazolones are accounted for. Some related experiments with 2-cyanophenylthioacetic acid, in which various metoxazine derivatives were produced, are described in the preceding paper.

Experimental.

Reactions of 2-Carboxyphenylthioacetamides with Potassium Acetate and Acetic Anhydride.—(1) 2-Carboxyphenylthioacetamide (McClelland, Rose, and Bartlett, *loc. cit.*) (3 g.), heated with freshly fused potassium acetate (3·7 g.) and acetic anhydride (16 c.c.) at 110° for ½ hour, yielded the steam-volatile products 3-acetoxy- and 3-hydroxy-2-acetylthionaphthen together with 3-hydroxy-2-acetylcarbamylthionaphthen.

(2) When this reaction was repeated but with sodium propionate and propionic anhydride and the products were distilled in steam, the residual solution on acidification gave *3-hydroxy-2-propionylcarbamylthionaphthen*, crystallising from alcohol in white needles, m. p. 188° (Found: C, 57·9; H, 4·4. $C_{12}H_{11}O_3NS$ requires C, 57·8; H, 4·4%). The substance gives a green-blue colour with ferric chloride and is readily oxidised by alkaline ferricyanide to thioindigo. Acetylation with acetic anhydride in boiling toluene yielded the O-*acetyl* derivative, crystallising from ether in long fibrous needles, m. p. 80° (Found: C, 57·7; H, 4·5. $C_{14}H_{13}O_4NS$ requires C, 57·7; H, 4·5%).

The products which distilled in steam were extracted with aqueous sodium hydroxide, the alkaline solution depositing on acidification 3-hydroxy-2-propionylthionaphthen, m. p. 73° (Krollpfeifer and Schneider, *Ber.*, 1928, **61**, 1284). The insoluble portion was recovered as a red oil identified as 3-propoxythionaphthen. It gave no colour with ferric chloride and was readily oxidised to thioindigo by ferricyanide; heated with aniline at 100° for 1 hour, it yielded propanilide, m. p. 103°, and heated with phenylhydrazine for 1 hour at 100°, furnished thionaphthindole, m. p. 253°.

When 2-carboxyphenylthioacetamide was heated with propionic anhydride alone at 140° for 1 hour the same 3-hydroxy-2-propionylcarbamylthionaphthen was the sole product. This substance, heated with sodium propionate and propionic anhydride at 140° for 2 hours, gave 3-hydroxy-2-propionylthionaphthen and 3-propoxythionapthen. The latter, carefully purified by washing its ethereal solution with alkali and water, the solution being then dried and evaporated, was heated with sodium propionate and propionic anhydride at 140° for 3 hours. No trace of 3-hydroxy-2-propionylthionaphthen could be detected in the resulting mixture.

(3) *o*-Mercaptobenzoic acid (4·5 g.) in aqueous sodium hydroxide (2·3 g.) was heated for ½ hour on the water-bath with *ω*-chloroacetanilide (5·g.), and the product precipitated by acidification. *2-Carboxyphenylthioacetanilide* was thus isolated (yield 90%), crystallising from alcohol in white needles, m. p. 220° (Found: C, 63·1; H, 4·3; N, 4·8. $C_{15}H_{13}O_3NS$ requires C, 62·7; H, 4·5; N, 4·9%). This acid was unaffected by heating in boiling toluene with phosphoric oxide. Heated with acetic anhydride, it yielded only 2-bis-(3-acetoxythionaphthen), m. p. 166°.

When *o*-carboxyphenylthioacetanilide was heated at 110° for ½ hour with acetic anhydride and potassium acetate the products volatile in steam were 3-hydroxy-2-acetyl- and 3-acetoxy-thionaphthen, the residue being 3-hydroxy-2-phenylcarbamylthionaphthen, m. p. 235° (Bartlett and McClelland, *loc. cit.*).

(4) Condensation of *o*-mercaptobenzoic acid with *ω*-chloroacetbenzylamide (Jacobs and Heidelberger, *J. Biol. Chem.*, 1915, **20**, 685) gave *2-carboxyphenylthioacetbenzylamide*, crystallising from alcohol in needles, m. p. 186° (Found: C, 64·0; H, 4·9. $C_{16}H_{15}O_3NS$ requires C, 63·8; H, 5·0%). When this substance was heated for ½ hour at 130° with acetic anhydride and potassium acetate the products were 3-hydroxy-2-acetyl-, 3-acetoxy- and 3-hydroxy-2-benzylcarbamyl-thionaphthen (m. p. 132°; Bartlett and McClelland, *loc. cit.*).

(5) Condensation of *o*-mercaptobenzoic acid with *ω*-chloroacetylbenzamide (Abderhalden and Reisz, *Fermentforschung*, 1930, **12**, 180—222, furnished *2-carboxyphenylthioacetylbenzamide*, crystallising from dioxan in small needles, m. p. 224° (Found: C, 61·2; H, 4·2. $C_{16}H_{13}O_4NS$ requires C, 61·0; H, 4·1%). This compound, when heated at 110° for ½ hour with potassium acetate and acetic anhydride, yielded 3-hydroxy-2-acetyl-, 3-acetoxy-, and (not volatile in steam) 3-hydroxy-2-acetylcarbamyl-thionaphthen (m. p. 204°).

Reactions of 2-Carbamylphenylthioacetic Acids and Their Derivatives with Potassium Acetate and Acetic Anhydride.—(1) *2-Carbamylphenylthioacetic acid* was prepared from *o*-mercaptobenzamide (compare D.R.-P. 570,364) (yield 73%). It formed colourless needles, m. p. 207°, from water (Found: N, 6·6. $C_9H_9O_3NS$ requires 6·6%). Oxidation in 2N-acetic acid with hydrogen peroxide (5 c.c. of 90-vol. per g.) at 100° yielded *2-carbamylphenylsulphinylacetic acid*, colourless needles, m. p. 210° (Found: C, 47·4; H, 4·3. $C_9H_9O_4NS$ requires C, 47·6; H, 4·0%). With hydrogen peroxide (90-vol., 2·5 c.c. per g.) in glacial acetic acid at 100° the sulphone was produced. By successive crystallisation from hot water and methanol, *2-carbamylphenylsulphonylacetic acid* was obtained in needles, m. p. 176—178° (Found: C, 44·4; H, 3·5; N, 5·5. $C_9H_9O_5NS$ requires C, 44·4; H, 3·7; N, 5·8%). This substance separates

from water in colourless prisms, m. p. *ca.* 137°, of the *monohydrate* (Found : H_2O, 7·0. $C_9H_9O_3NS,H_2O$ requires H_2O, 6·9%).

When 2-carbamylphenylthioacetic acid was heated for ½ hour at 105° with potassium acetate and acetic anhydride the products identified were 3-hydroxy-2-acetyl-, 3-acetoxy-, and 3-hydroxy-2-acetylcarbamyl-thionaphthen.

The corresponding *ethyl 2-carbamylphenylthioacetate*, obtained from 2-mercaptobenzamide and ethyl chloroacetate, forms colourless needles from hot water, m. p. 97° (Found : C, 55·1; H, 5·4; S, 13·3. $C_{11}H_{13}O_3NS$ requires C, 55·2; H, 5·4; S, 13·4%). When this ester was heated with potassium acetate and acetic anhydride at 145—150° for ½ hour, no steam-volatile products were found. The main product was *ethyl 3-acetoxythionaphthen-2-carboxylate*, m. p. 105°, identical with that obtained by acetylation of 3-hydroxythionaphthen-2-carboxylate (Found : C, 58·8; H, 4·3; S, 12·0. $C_{13}H_{12}O_4S$ requires C, 59·1; H, 4·5; S, 12·1%). It is insoluble in acid or alkali, gives no ferric chloride reaction, is not oxidised to thioindigo by ferricyanide, and yields on heating with aniline ethyl 3-hydroxythionaphthen-2-carboxylate, m. p. 74°, and acetanilide. In addition, the main condensation yielded a little ethyl hydroxythionaphthencarboxylate and a yellow oil which proved to be ethyl 3-acetamidothionapthen-2-carboxylate, hydrolysed to 3-amino-2-carboxythionaphthen (see *Annalen*, 1907, **351**, 416). This substance gave with acetic anhydride, or in benzene solution with acetyl chloride, the N-*acetyl* derivative, crystallising from glacial acetic acid in colourless needles, m. p. 230° (Found : C, 56·2; H, 3·7. $C_{11}H_9O_3NS$ requires C, 56·2; H, 3·8%), and unchanged by heating with acetic anhydride and potassium acetate. The identity of the aminocarboxythionaphthen was also confirmed by its conversion into 3-hydroxythionaphthen on distillation with dilute sulphuric acid.

When ethyl carbamylphenylthioacetate was heated with acetic anhydride alone at 140—145° for ½ hour, ethyl 3-hydroxythionaphthen-2-carboxylate and ethyl 3-acetamidothionaphthen were again obtained.

2-Carbamylphenylthioacetic acid (10 g.) was boiled with acetic anhydride (15 c.c.) in toluene (100 c.c.) until solution was complete (3—5 hours). Light petroleum (200 c.c.) was added to the cold solution, and the mixture left for 24 hours. The product which separated was the cyclic *imide*, which formed colourless needles from dilute acetic acid, m. p. 143° (yield 60%) (Found : C, 55·9; H, 3·6; N, 7·2; *M*, ebullioscopic in benzene, 197. $C_9H_7O_2NS$ requires C, 56·0; H, 3·6; N, 7·3%; *M*, 193). The same product was obtained by heating with propionic anhydride at 100°.

The imide is soluble in organic solvents and in hot aqueous acetic acid. It dissolves in cold aqueous sodium hydroxide and is reprecipitated on acidification, but it is not dissolved by aqueous ammonia or sodium hydrogen carbonate. It gave no colouration with ferric chloride or alkaline potassium ferricyanide. Heated in boiling water for 6 hours, it was hydrolysed to the parent carbamylphenylthioacetic acid. It was unaffected by boiling aniline, by *p*-toluenesulphonyl chloride in hot pyridine, by diazomethane in ether, and by nitrous acid. Warmed with resorcinol and sulphuric acid, it yields an orange solution which, on dilution and being made alkaline, shows a green fluorescence.

The formation of this imide could not be detected when 2-carboxyphenylthioacetamide was heated at 110° with acetic anhydride for 1 hour or for shorter times, the only product found being 3-hydroxy-2-acetylcarbamylthionaphthen, m. p. 203°.

When the imide was heated at 110° for 20 minutes with potassium acetate and acetic anhydride it reacted vigorously to produce 3-hydroxy-2-acetyl-, 3-acetoxy-, and 3-hydroxy-2-acetylcarbamyl-thionaphthen.

Addition of alcoholic potassium ethoxide to a solution of the imide in dioxan yielded the *potassium* salt as a microcrystalline powder which was washed with alcohol and benzene and dried in a vacuum (Found : K, 16·7. $C_9H_6O_2NSK$ requires K, 16·9%). Heated in a sealed tube at 100° for 3 hours with methyl iodide (3 mols.), it gave the N-*methylimide*, crystallising from alcohol in colourless needles, m. p. 97° (yield 56%) (Found : C, 58·1; H, 4·4. $C_{10}H_9O_2NS$ requires C, 58·0; H, 4·3%). This substance is insoluble in cold dilute alkali, but is hydrolysed on boiling to 2-methylcarbamylphenylthioacetic acid, m. p. 146°. It gives no colour with ferric chloride or alkaline ferricyanide.

Heated at 100° for 6 hours with potassium acetate and acetic anhydride, the *N*-methylimide gave a mixture, containing no steam-volatile thionaphthens, from which, by extraction with aqueous ammonium carbonate and acidification of the solution, 3-hydroxy-2-methylcarbamylthionaphthen, m. p. 123° (Bartlett and McClelland, *loc. cit.*) was isolated, which gave the characteristic reactions of this substance.

The N-*ethylimide*, from the potassium salt and ethyl bromide in a sealed tube, crystallised from aqueous alcohol (charcoal) in colourless prisms, m. p. 72° (yield, 42%) (Found : C, 59·9; H, 4·9. $C_{11}H_{11}O_2NS$ requires C, 59·7; H, 5·0%).

(2) 2 : 2′-Dithiobenzomethylamide (10 g.) was reduced with zinc dust (10 g.) and alcoholic hydrochloric acid in a current of nitrogen, and the filtered solution evaporated under reduced pressure. The solid product was condensed with sodium chloroacetate (8 g.) in aqueous sodium hydroxide (125 c.c., 2N) at 100° for ½ hour. Acidification gave a precipitate of 2-*methylcarbamylphenylthioacetic acid*, colourless needles, m. p. 146°, from alcohol (Found : C, 53·4; H, 5·3. $C_{10}H_{11}O_3NS$ requires C, 53·3; H, 4·9%). Heated with potassium acetate and acetic anhydride at 100° for 6 hours, it yielded 3-acetoxythionaphthen and a trace of 3-hydroxy-2-acetylthionaphthen.

(3) From 2 : 2′-dithiobenzoethylamide was obtained 2-*ethylcarbamylphenylthioacetic acid* (yield, 65%) as colourless prisms, m. p. 125°, from aqueous acetic acid (Found : C, 55·4; H, 5·6. $C_{11}H_{13}O_3NS$ requires C, 55·2; H, 5·4%). Heated at 100° for 3 hours with potassium acetate and acetic anhydride, it yielded 3-acetoxy-1-thionaphthen, 2-bis-(3-acetoxythionaphthen), m. p. 166°, and by extraction with ammonium carbonate and acidification, 3-hydroxy-2-ethylcarbamylthionaphthen of m. p. 133° and showing the characteristic reactions of this substance (Bartlett and McClelland, *loc. cit.*).

(4) 2-*Benzylcarbamylphenylthioacetic acid*, obtained from 2 : 2′-dithiobenzobenzylamide (yield, 72%), forms colourless needles, m. p. 142°, from aqueous acetic acid (Found : C, 63·9; H, 5·1. $C_{16}H_{15}O_3NS$ requires C, 63·8; H, 5·0%). This acid was heated at 100° for 4 hours with acetic anhydride (2 parts) and potassium acetate (½ part), the mixture poured into water, and 3-acetoxythionaphthen removed in a current of steam. The residual brown oil was washed with water, boiled with 50% acetic acid, and the

solution evaporated under diminished pressure. The material was dissolved in ether and extracted with aqueous N-sodium hydroxide. The alkaline solution furnished unchanged 2-benzylcarbamylphenylthioacetic acid and 3-hydroxy-2-benzylcarbamylthionaphthen. The ethereal solution was washed successively with dilute acid and water, dried over sodium sulphate, and evaporated. The viscous brown oil remaining was further purified by charcoal in 90% alcohol, the solution evaporated at 100°, and the oil dried in a vacuum for 3 days. The N-*benzylimide* was thus obtained as an oil which could not be distilled under diminished pressure (Found: C, 62·7; H, 4·8; S, 11·2. $C_{16}H_{13}O_3NS$ requires C, 67·8; H, 4·6; S, 11·3%). It was hydrolysed to the parent acid by standing for 3 days with cold alcoholic 5% sodium hydroxide.

When the benzylcarbamylphenylthioacetic acid was heated with potassium acetate and acetic anhydride at 100° for 9 hours the products isolated were 3-acetoxythionaphthen and 3-hydroxy-2-benzylcarbamylthionaphthen, m. p. 130°. The *N*-benzylimide with the same reagents under similar conditions furnished the same products.

A separate experiment showed that the acid was recovered unchanged after standing for 3 days in alcholic sodium hydroxide solution.

(5) 2-*Phenylcarbamylphenylthioacetic acid*, obtained from 2 : 2′-dithiobenzanilide (yield, 73%), crystallised from aqueous alcohol in white plates, m. p. 137° (Found: C, 63·0; H, 4·6. $C_{15}H_{13}O_3NS$ requires C, 62·7; H, 4·5%). Heated with potassium acetate and acetic anhydride at 110—115° for 20 minutes, it yielded 3-hydroxy-2-acetyl-, 3-acetoxy-, and 3-hydroxy-2-phenylcarbamyl-thionaphthen (Bartlett and McClelland *loc. cit.*).

The acid (1 part) was heated at 100° for 5 hours with acetic anhydride (2 parts), and excess of the latter removed by three extractions with light petroleum. The residual oil was purified by solution in toluene and precipitation with light petroleum, followed by the action of charcoal in alcoholic solution, and finally it was recovered and kept in a vacuum for 2 days. The N-*phenylimide* was thus obtained as an oil which could not be distilled (Found: S, 11·6. $C_{15}H_{11}O_3NS$ requires S, 11·9%). It was not immediately soluble in dilute alkali but dissolved on standing for 15 minutes and the solution on acidification deposited the parent acid once more. Heated at 100° for 1 hour with potassium acetate and acetic anhydride, it gave the same three substances as were obtained from the acid under similar conditions.

3-Hydroxy-2-phenylcarbamylthionaphthen was also heated with potassium acetate and acetic anhydride for ½ hours at 110°. 3-Hydroxy-2-acetyl- and 3-acetoxy-thionaphthen were removed in a current of steam, and the residue yielded mainly N-*acetylphenylcarbamyl-3-acetoxythionaphthen*, white plates from alcohol, m. p. 138° (Found: S, 8·7. $C_{19}H_{15}O_4NS$ requires S, 9·1%). It yielded on alkaline hydrolysis 3-hydroxy-2-phenylcarbamylthionaphthen, and the latter was also present in the mother-liquors of the preparation. A little 3-hydroxy-1-thionaphthen was also formed.

KING'S COLLEGE, STRAND, W.C.2. [*Received, February 25th*, 1947.]

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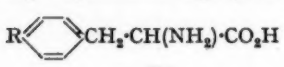
20. *Bacteriostasis in the Amino-acid Series. Part I. Derivatives of Alanine.*

By D. F. ELLIOTT, A. T. FULLER, and C. R. HARINGTON.

It is known that inhibition of bacterial growth can be effected by structural analogues of naturally occurring amino-acids; it is also known that all natural aromatic and heterocyclic amino-acids are β-substituted alanines. These considerations led to a search for antibacterial activity among alanines substituted in the β-position by pyridine, quinoline, and basic derivatives of benzene. The compounds so far studied are *p*-aminophenyl-, ω-amino-*p*-tolyl-, and *p*-dimethylaminophenyl-alanine, β-pyridyl(4)alanine, β-quinolyl(4)alanine, and the 6-methoxy-derivative of the last. Significant inhibitory actions have been observed with three only of these compounds, namely β-ω-amino-*p*-tolylalanine, β-6-methoxyquinolyl(4)alanine, and β-pyridyl(4)alanine; these inhibit hæmolytic streptococcus in broth in the range 1 : 2000 to 1 : 5000, and the last shows some action against *B. coli* in synthetic medium.

ONE of the main requirements of a satisfactory chemotherapeutic agent is that it should readily penetrate or be absorbed by the micro-organism against which it is directed. It occurred to us that such penetration might be facilitated if the drug were to contain an α-amino-acid grouping; moreover, since all naturally occurring aromatic and heterocyclic amino-acids are β-substituted alanines it was to this particular series of compounds that our attention was first directed. It is already known that some degree of inhibition of bacterial growth, presumably of a competitive character, can be effected by close structural analogues of essential natural amino-acids; examples are the antagonism of phenylalanine by β-thienyl(2)alanine (Dittmer, Ellis, McKennis, and du Vigneaud, *J. Biol. Chem.*, 1946, **164**, 761) and that of methionine by methoxinine (Roblin, Lampen, English, Cole, and Vaughan, *J. Amer. Chem. Soc.*, 1945, **67**, 290). Our own aim has been not so much to develop this type of competitive growth inhibition by closely related analogues of amino-acids but rather to study the effect of compounds in which the characteristic α-aminopropionic acid side-chain is attached through its β-carbon atom to benzene carrying a basic substituent or basic heterocyclic nuclei.

As a preliminary exploration of this idea we have studied *p*-aminophenylalanine (I; R = NH_2), β-ω-*amino*-p-*tolylalanine* (I; R = $NH_2 \cdot CH_2$), β-p-*dimethylaminophenylalanine* (I; R = NMe_2), β-pyridyl(4)alanine (II), β-*quinolyl*(4)*alanine* (III; R = H) and β-6-*methoxyquinolyl*(4)*alanine* (III; R = MeO). Extension to the *p*-guanidino- and *p*-amidino-derivatives of phenylalanine is projected.



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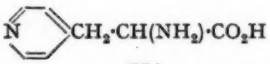

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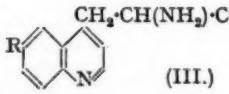
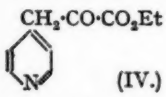


(III.)

p-Aminophenylalanine was prepared according to Erlenmeyer and Lipp (*Annalen*, 1883, **219**, 219). For the synthesis of ω-amino-*p*-tolylalanine, *p*-cyanobenzyl chloride (Mellinghoff, *Ber.*, 1889, **22**, 3208) was condensed with ethyl acetamidomalonate, and the product hydrogenated by the method of Hartung (*J. Amer. Chem. Soc.*, 1928, **50**, 3370) to give *ethyl acetamido*-p-*aminomethylbenzylmalonate hydrochloride*, hydrolysis of which afforded the desired amino-acid. p-*Dimethylaminophenylalanine* was prepared by the Erlenmeyer synthesis as modified by Harington and McCartney (*Biochem. J.*, 1927, **21**, 852), starting with *p*-dimethylaminobenzaldehyde.

The alanine derivatives in the pyridine and quinoline series were synthesised by a method which seems to be generally applicable to amino-acids of this type, and which may be exemplified by the preparation of β-pyridyl(4)alanine. γ-Picoline was condensed with ethyl oxalate (cf. the condensation with lepidine, Wislicenus and Kleisinger, *Ber.*, 1909, **42**, 140) to give the potassium derivative of *ethyl pyridyl*(4)*pyruvate* (IV); this was converted successively into the *oxime* (V; R = Et) and the *oximino-acid* (V; R = H), which was finally reduced to give the desired



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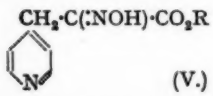

(V.)

amino-acid (II). The initial condensation with ethyl oxalate proceeded satisfactorily with lepidine and 6-methoxylepidine, but with γ-picoline the yield obtained was very poor, even when pyridine was added to the reaction mixture (cf. Grundmann, *Ber.*, 1937, **70**, 1148; Elks, Elliott, and Hems, *J.*, 1944, 629; Blout, Fried, and Elderfield, *J. Org. Chem.*, 1943, **8**, 37). For the final reduction of the oximino-acids catalytic methods were first tried, but without great success, the process being incomplete with palladium black in aqueous ammonia and very slow with Raney nickel. The latter case was complicated by the passage of nickel ions into solution and by the formation of amorphous by-products. The well-known method of reduction using palladised charcoal in alcoholic hydrogen chloride was also unsuccessful. The preparative problem was satisfactorily solved by reduction with stannous chloride in cold hydrochloric acid solution. The formation of amorphous products is probably due to polymerisation of dihydro-derivatives formed by partial reduction of the heterocyclic ring (see Bergstrom, *Chem. Reviews*, 1944, **35**, 162). This phenomenon was particularly marked with the pyridine derivative which, in presence of Raney nickel, absorbed 1 mol. of hydrogen only to give a completely amorphous product (cf. Adkins, Kuick, Farlow, and Wojeik, *J. Amer. Chem. Soc.*, 1934, **56**, 2425).

The pyridyl and quinolyl derivatives of alanine behave abnormally with ninhydrin. It was stated by Niemann, Lewis, and Hays (*J. Amer. Chem. Soc.*, 1942, **64**, 1678), who synthesised β-pyridyl(4)alanine in minute yield by a method different from that described in this paper, that the colour given by this amino-acid on heating with ninhydrin was red. We have confirmed this observation and have found that it also applies to the quinoline derivatives if the test is carried out in the ordinary way, *i.e.*, in aqueous or aqueous pyridine solution. If on the other hand pure pyridine or pyridine containing only a trace of water is used the normal blue colour is given by the quinolylalanines, although even under these conditions the colour given by pyridylalanine remains red [cf. the behaviour of proline (Grassman and von Arnim, *Annalen*, 1934, **509**, 288)].

Biological Results.

The amino-acids mentioned above have been tested for bacteriostatic activity by the methods usually employed in this laboratory, and the results are summarised in the Table. It will be seen that significant activity against *Strep. pyogenes*, Group A in broth is shown by ω-amino-*p*-tolylalanine, β-6-methoxyquinolyl(4)alanine, and β-pyridyl(4)alanine; the last compound is also fairly active against *B. coli* in synthetic medium. The inhibitory activity of *p*-aminophenylalanine is antagonised not only by phenylalanine, which is a possible direct

competitor, but by other amino-acids such as asparagine, lysine, and a mixture of glycine, glutamic acid, and arginine; this probably accounts for the fact that *p*-aminophenylalanine is apparently more active against *B. coli* than against *Staph. aureus*, since the synthetic medium in the latter case contained amino-acids (hydrolysed casein) and in the former did not.

Minimum inhibitory concentrations (*mg.*/100 *c.c.*).

	Strep. pyogenes Group A.		*Staph. aureus.*		*B. coli.*	
	Blood.	Broth.	Synthetic.	Broth.	Synthetic.	Broth.
p-Aminophenylalanine	>500	>1000	1000	>1000	200	>1000
p-Dimethylaminophenylalanine	>500	500	1000	>1000	1000	>1000
ω-Amino-*p*-tolylalanine dihydrochloride	>500	50	>1000	>1000	1000	>1000
β-Quinolyl(4)alanine	500	500	1000	>1000	500	>1000
β-6-Methoxyquinolyl(4)alanine	200	35	>1000	>1000	1000	>1000
β-Pyridyl(4)alanine dihydrochloride	200	20	>1000	>1000	75	1000

The compounds were also tested against acid-fast organisms but showed no activity. The two quinolylalanines were tested in addition against *E. histolytica*, but again showed no activity. We are indebted to Dr. P. D'Arcy Hart and Dr. J. D. Fulton respectively for carrying out these tests.

Experimental.

Ethyl Acetamido-p-*cyanobenzylmalonate.*—Sodium (1·15 g.; 1/20 atom) was dissolved in dry alcohol (25 c.c.); the solution was cooled somewhat and treated with ethyl acetamidomalonate (10·9 g.; 1/20 mol.) followed by *p*-cyanobenzyl chloride (Mellinghoff, *loc. cit.*) (8 g.; 5% excess over 1/20 mol.). The mixture was refluxed for 2 hours; the product had then separated as a crystalline mass. After addition of water (200 c.c.) to the cooled product it was filtered off and dried in a desiccator. Yield, 15·6 g. (94%). The *ester* formed long colourless needles from alcohol or acetone, m. p. 167° (Found: N, 8·7. $C_{17}H_{20}O_5N_2$ requires N, 8·4%).

Ethyl Acetamido-p-*aminomethylbenzylmalonate Hydrochloride.*—The cyano-compound (10 g.) was suspended in a mixture of absolute alcohol (200 c.c.) and absolute alcoholic hydrogen chloride (2·7N; 35 c.c.) and hydrogenated at room temperature and 100 atmospheres' pressure in the presence of palladium charcoal catalyst (10 g.) prepared according to Iwamoto and Hartung (*J. Org. Chem.*, 1944, **9**, 514). After 5 hours no further absorption of hydrogen took place. After removal of the catalyst the filtrate was evaporated to small bulk under reduced pressure. Dry ether (500 c.c.) was added to the crystalline mass. After 12 hours at room temperature the *hydrochloride* (yield, 6·5 g.; 70% on cyano-compound consumed) was filtered off, washed with dry ether, and crystallised from alcohol, from which it separated in elongated rectangular plates, m. p. 211—212° (decomp.) (Found: C, 54·45; H, 6·8. $C_{17}H_{25}O_5N_2Cl$ requires C, 54·8; H, 6·8%). Unchanged cyano-compound (1·6 g.) was recovered from the ethereal filtrate by evaporation and also from the catalyst by extraction with acetone. The catalyst could be used several times for this reduction. Treatment of a concentrated aqueous solution of the hydrochloride with sodium acetate yielded the *acetate* which crystallised from alcohol in fine needles, m. p. 163—164° (Found: N, 7·25. $C_{19}H_{28}O_7N_2$ requires N, 7·1%).

Ethyl Acetamido-p-*aminomethylbenzylmalonate* was liberated from the hydrochloride by treatment with two equivalents of ice-cold N-sodium hydroxide and extraction with chloroform. It had a strongly alkaline reaction and formed long rectangular plates, m. p. 86—87° (Found: N, 8·5. $C_{17}H_{24}O_5N_2$ requires N, 8·3%).

β-ω-Amino-p-*tolylalanine Derivatives.*—The above-described amine acetate (3 g.) was refluxed for 4 hours with 3N-hydrochloric acid (50 c.c.) and the solution evaporated to dryness under reduced pressure. The solid residue was dissolved in hot water (15 c.c.) and neutralised to pH 5 with concentrated ammonia solution.

β-ω-Amino-p-*tolylalanine monohydrochloride* separated on cooling in clusters of stout prisms. A second crop of crystals was obtained by evaporation of the mother liquors. Yield, 1·2 g. (71%). The compound was extremely stable to heat; it did not melt at 360° and even at this temperature turned only slightly brown (Found: N, 12·0; 12·2; Cl, 15·8. $C_{10}H_{15}O_2N_2Cl$ requires N, 12·15; Cl, 15·4%).

β-ω-Amino-p-*tolylalanine dihydrochloride*, obtained by treating a hot concentrated solution of the monohydrochloride with concentrated hydrochloric acid and allowing it to cool, separated in hydrated form and had m. p. 266—268° (with foaming). It was dried at 100°/20 mm. before analysis (Found: N, 10·2. $C_{10}H_{16}O_2N_2Cl_2$ requires N, 10·5%). When ethyl acetamido-*p*-aminomethylbenzylmalonate hydrochloride (2·7 g.) was refluxed for 5 hours with 2N-sulphuric acid (25 c.c.) and the solution evaporated to small bulk under reduced pressure at low temperature, *β-ω-amino*-p-*tolylalanine bis*(*hydrogen sulphate*) (1·5 g.) separated in colourless plates, m. p. 209—210° (decomp.) (Found: N, 7·1. $C_{10}H_{18}O_{10}N_2S_2$ requires N, 7·2%). The sulphate was dissolved in water and sulphuric acid removed with several times recrystallised barium hydroxide (cf. Vickery and Leavenworth, *J. Biol. Chem.*, 1928, **76**, 437). The filtrate, which was strongly alkaline, was allowed to evaporate in a desiccator, leaving *β-ω*-amino-*p*-tolylalanine as a crystalline mass which resisted attempts at recrystallisation.

2-*Phenyl*-4-p-*dimethylaminobenzylidene*-5-*oxazolone.** *p*-Dimethylaminobenzaldehyde (15 g.), hippuric acid (18 g.), freshly fused sodium acetate (8·2 g.), and acetic anhydride (30 c.c.) were mixed and well stirred by hand while being heated at 100° for 20 minutes. The red mass was cooled, rubbed with

* Hellerman, Porter, Lowe, and Koster (*J. Amer. Chem Soc.*, 1946, **68**, 1890) refer to a red azlactone, and the corresponding cinnamic acid, identical with ours, prepared by a method as yet unpublished.

cold water, filtered, and the residue washed with spirit to remove tarry material and finally washed with ether. The bright red *oxazolone* (16·8 g.; 57·5%) crystallised from benzene in long red needles, m. p. 213—214° (Found: C, 73·8; H, 5·3; N, 9·7. $C_{18}H_{16}O_2N_2$ requires C, 74·0; H, 5·5; N, 9·6%). The azlactone was soluble in cold concentrated hydrochloric acid and insoluble in dilute hydrochloric acid (3N) in the cold, but it rapidly dissolved on boiling. When this solution was neutralised with ammonia until just acid to litmus, *α-benzamido-*p*-dimethylaminocinnamic acid* separated as a yellow precipitate. It formed bright yellow prisms from alcohol, m. p. 225—226° (decomp.) (Found: C, 69·8; H, 5·2; N, 9·25. $C_{18}H_{18}O_3N_2$ requires C, 69·7; H, 5·8; N, 9·0%). The cinnamic acid was easily soluble in acid and alkali.

*β-*p*-Dimethylaminophenylalanine.*—The azlactone (5 g.) was refluxed 1½ hours with a mixture of acetic anhydride (25 c.c.) and hydriodic acid (*d* 1·7; 25 c.c.) (previously prepared by adding the anhydride slowly to the hydriodic acid with cooling) and red phosphorus (5 g.). After cooling, the solution was diluted, filtered, and evaporated to dryness under reduced pressure. The residual syrup rapidly crystallised and was dissolved in hot water (50 c.c.) and made faintly alkaline with concentrated ammonia solution. The *amino-acid* separated as colourless plates (2·9 g.; 82%). After recrystallisation from hot water, in which it was not very soluble, the product had m. p. 256—258° (decomp.). It was dried at 100°/20 mm. for 3 hours before analysis (Found: C, 63·7; H, 7·6; N, 13·4. $C_{11}H_{16}O_2N_2$ requires C, 63·4; H, 7·7; N, 13·5%).

α-Oximino-β-pyridyl(4)propionic Acid.—Dry potassium ethoxide was prepared by adding clean potassium (3·9 g.; 1/10 atom) to the minimum quantity of dry alcohol and evaporating the solution to dryness under reduced pressure over a cool flame with swirling of the flask to spread the solid evenly over the walls. The flask was then immersed up to the neck in an oil-bath at 180°, and heating continued for 15 minutes at 20 mm. After cooling in a vacuum, dry ether (250 c.c.) was added, followed immediately by ethyl oxalate (14·6 g.; 1/10 mol.), the mixture being gently shaken. The solution of the ethoxide was treated with γ-picoline (9·3 g.; 1/10 mol.) and dry pyridine (50 c.c.), and the mixture refluxed in a nitrogen atmosphere for 48 hours in a bath at 45—50°. The yellow potassium salt, which was very hygroscopic, was collected, washed with dry ether, and dried in a desiccator. Yield, 4 g. (17·3%). The salt was added to ice-cold, oxygen-free N-hydrochloric acid (20 c.c.) and then a mixture of hydroxylamine hydrochloride (1·2 g.) and potassium acetate (2·0 g.) in a small quantity of water was added in small portions with warming to about 50° for a few minutes. On cooling, crystals of *ethyl α-oximino-β-pyridyl(4)propionate* separated, and further crops were obtained on evaporation of the mother liquors at low temperature. Yield, 2·5 g. (12% calculated on γ-picoline). The ester formed orange prisms from ethyl acetate, m. p. 146—147° (Found: N, 13·3. $C_{10}H_{12}O_3N_2$ requires N, 13·5%). It dissolved easily in 1 equiv. of N-sodium hydroxide in the cold and was reprecipitated unchanged on neutralisation with acid. When the ester (3·8 g.) was boiled for 5 minutes with N-sodium hydroxide (21·4 c.c.; 2 equivs.), neutralised while warm with 5N-hydrochloric acid (4·3 c.c.), filtered rapidly from a small amount of red pigment, and kept 2 days at 0°, *α-oximino-β-pyridyl(4)propionic acid* separated, and a further crop was obtained from the mother liquors on evaporation. Yield, 2·2 g. (67%). The oximino-acid formed buff-coloured plates from hot water, m. p. 178° (decomp.) (Found: N, 15·5. $C_8H_8O_3N_2$ requires N, 15·6%).

β-Pyridyl(4)alanine Dihydrochloride.—The oximino-acid (0·9 g.) was added to a solution of stannous chloride (2·5 g.) in concentrated hydrochloric acid (10 c.c.). The oxime rapidly dissolved and gave a light brown solution. After 24 hours the solution was diluted to 300 c.c. and tin removed with hydrogen sulphide. The filtrate afforded a mass of heavy crystals on evaporation (0·82 g.; 68%). The *β-pyridyl(4)alanine dihydrochloride* separated in massive prisms when a hot concentrated solution in 3N-hydrochloric acid was treated with several parts of boiling alcohol. It had m. p. 229—230° (decomp.) (Found: C, 40·6; H, 5·1; N, 11·6. $C_8H_{12}O_2N_2Cl_2$ requires C, 40·2; H, 5·1; N, 11·7%).

α-Oximino-β-quinolyl(4)propionic Acid.—The corresponding pyruvic ester was prepared by condensation of lepidine with ethyl oxalate essentially according to Wislicenus and Kleisinger (*loc. cit.*) except that the reaction mixture was kept for 48 hours instead of 24 hours as stated by these authors. The crude finely powdered ester (2·4 g.; 1/100 mol.) was added to a mixture of fused sodium acetate (1 g.; 1/80 mol.) and hydroxylamine hydrochloride (0·7 g.; 1/100 mol.) in water (2 c.c.), and following addition of alcohol (25 c.c.) the whole was refluxed for 30 minutes. After cooling and addition of water (50 c.c.) the *ethyl α-oximino-β-quinolyl(4)propionate* (2·15 g.; 84·5%) was collected and crystallised from spirit. It formed sheaves of colourless prisms, m. p. 183° (Found: N, 11·0. $C_{14}H_{14}O_3N_2$ requires N, 10·85%).

α-Oximino-β-quinolyl(4)propionic acid was prepared by refluxing the ester (1·2 g.) for ten minutes with N-sodium hydroxide (10 c.c.) and acidifying while hot with excess of glacial acetic acid. After cooling, the yellow crystals were filtered off and dried in a desiccator. Yield, 1·05 g. (98%); m. p. 204° (decomp.) (Found: N, 12·2. $C_{12}H_{10}O_3N_2$ requires N, 12·2%).

β-Quinolyl(4)alanine and Derivatives.—(*a*) The above oximino-acid (1·15 g.) was dissolved by warming with N-ammonia (50 c.c.) and hydrogenated at room temperature and pressure in the presence of Raney nickel (0·25 g.). Fresh catalyst (0·25 g.) was added after 4 hours, and shaking continued for 24 hours; the theoretical amount of hydrogen had then been absorbed. The greenish solution, in which was suspended some amorphous material found to be extremely tedious to remove by filtration or centrifugation, was decanted from the catalyst and evaporated to dryness under reduced pressure. The residue was dissolved in boiling water and nickel ions removed with hydrogen sulphide. On evaporating the filtrate to small volume *β-quinolyl(4)alanine* was obtained as a bulky mass of almost colourless needles (0·74 g.; 68·5%) which were filtered off and washed with absolute alcohol. The amino-acid had m. p. 248—250° (decomp.). It separated from hot water in varying degrees of hydration and was dried in the usual way for analysis (Found: C, 66·4; H, 5·9; N, 12·6. $C_{12}H_{12}O_2N_2$ requires C, 66·65; H, 5·6; N, 13·0%). The *dihydrochloride dihydrate* had m. p. 242—244° (decomp.) (Found: Cl, 21·1; loss at 60°/20 mm., 10·1. $C_{12}H_{14}O_2N_2Cl_2,2H_2O$ requires Cl, 21·8; loss for $2H_2O$, 11·1%). When the amino-acid (50 mg.) was added to 50% sulphuric acid (0·1 c.c.) it dissolved, and on standing overnight the *bis(hydrogen sulphate) monohydrate* (60 mg.) separated in aggregates of massive prisms, m. p. 202—204°

(decomp.) (Found: S, 15·1; loss at 100°/20 mm., 3·9. $C_{12}H_{16}O_{10}N_2S_2$ requires S, 14·9; loss for $1H_2O$, 4·3%).

(*b*) The oximino-acid (2·3 g.) was added, with shaking, to a solution of stannous chloride (5 g.) in concentrated hydrochloric acid (25 c.c.). The oxime dissolved slowly because of the formation of a sparingly soluble hydrochloride, and the solution was shaken mechanically at room temperature for 18 hours. The crystalline tin complex was filtered off, washed with a small quantity of cold concentrated hydrochloric acid and then with dry ether, and dissolved in water (300 c.c.). The yellow solution was treated with hydrogen sulphide to remove tin, and the filtrate evaporated to dryness under reduced pressure. The residual syrup rapidly solidified to a crystalline mass of the dihydrochloride dihydrate. Yield, 2·5 g. (76·9%). For comparison a small portion was warmed in a vacuum with excess of 50% sulphuric acid until most of the hydrogen chloride had been removed, and then cooled. The bis(hydrogen sulphate) monohydrate which separated was identical with the sample described in (*a*).

Ethyl 6-Methoxyquinolyl(4)pyruvate.—6-Methoxylepidine (Ainley and King, *Proc. Roy. Soc.*, **1938**, **125**, *B*, 84) (17·3 g.; 1/10 mol.) dissolved in a minimum amount of dry ether was added to a mixture of ethyl oxalate (15 c.c.), potassium ethoxide (from 3·9 g. of potassium; 1/10 atom), dry pyridine (50 c.c.), and absolute ether (250 c.c.) prepared as previously described, and the solution was kept for 3—4 days at room temperature. The orange potassium salt was collected, washed with dry ether, and dried in a desiccator. Yield, 17 g. (55%). *Ethyl 6-methoxyquinolyl(4)pyruvate* was liberated from this salt by shaking it thoroughly with 1 equiv. of 0·5N-hydrochloric acid, filtering off the solid, and drying it in a desiccator. It formed orange prisms from dioxan, m. p. 186—187° (decomp.) (Found: N, 5·1. $C_{15}H_{15}O_4N$ requires N, 5·4%).

α-Oximino-β-6-methoxyquinolyl(4)propionic Acid.—The corresponding *ethyl* ester was prepared as previously described for the unsubstituted quinoline compound and formed colourless hexagonal plates from alcohol, m. p. 222—223° (yield, 93%) (Found: C, 62·6; H, 5·6; N, 9·8. $C_{15}H_{16}O_4N_2$ requires C, 62·5; H, 5·6; N, 9·7%). *α-Oximino-β-6-methoxyquinolyl(4)propionic acid*, prepared in quantitative yield by hydrolysis in the usual way with sodium hydroxide, formed pale yellow spear-shaped prisms, m. p. 213—214° (decomp.). The compound darkened in bright light (Found: N, 10·4. $C_{13}H_{12}O_4N_2$ requires N, 10·8%).

β-6-Methoxyquinolyl(4)alanine.—(*a*) The oximino-acid behaved similarly to the unsubstituted quinoline compound on hydrogenation with Raney nickel catalyst. *β-6-Methoxyquinolyl(4)alanine* was thus obtained in 57% yield and formed fine needles from hot water, m. p. 258—260° (decomp.). It was dried at 110°/20 mm. before analysis (Found: C, 63·1; H, 6·2; N, 11·4. $C_{13}H_{14}O_3N_2$ requires C, 63·4; H, 5·7; N, 11·6%).

(*b*) The oximino-acid (5·2 g.) was reduced with stannous chloride as previously described. This oxime dissolved more readily and gave a clear solution from which the tin complex suddenly separated after shaking for 15 minutes. After being shaken for 3 hours the solution was cooled overnight at 0° and the product isolated as before. The pale yellow *β-6-methoxyquinolyl(4)alanine dihydrochloride monohydrate* (4·5 g.; 67%) separated from dilute hydrochloric acid in irregular masses of hexagonal plates, m. p. 212—214° (decomp.). It was identical with a sample from the amino-acid prepared by method (*a*) [Found: N, 8·0; loss at 100°/20 mm., 5·9. $C_{13}H_{16}O_3N_2Cl_2,H_2O$ requires N, 8·3; loss for $1H_2O$, 5·3. Found (on dried sample): C, 49·1; H, 5·15. $C_{13}H_{16}O_3N_2Cl_2$ requires C, 48·9; H, 5·1%].

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21. α-Methylenic Reactivity in Olefinic Systems. Part III. The Prins Reaction with Ethylene and α-Methylstyrene.

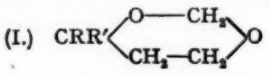
By John W. Baker.

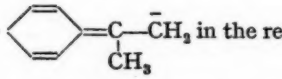
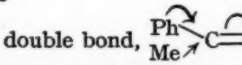
Ethylene reacts very slowly and incompletely with a mixture of 100% acetic–sulphuric acids and trioxymethylene at 80° to give a small yield of the diacetate of trimethylene glycol and a *substance*, b. p. 125°/0·8 mm., of the same empirical composition and acetyl content. α-Methylstyrene reacts readily at 0° with the same mixture to give the *diacetate*, b. p. 142°/0·5 mm., and the cyclic *formal*, m. p. 42°, of *3-phenylbutane*-1 : 3-*diol* (cf. Part I, *J.*, 1944, 296), together with the isomeric *substances A*, m. p. 202°, and *B*, m. p. 128°, the theoretically possible structures of which it has not been possible to establish experimentally. α-Methylenic activity in the olefin is structurally impossible in ethylene and, as expected, seems to be suppressed in α-methylstyrene. The effect of structural conditions in the olefin on the yield of the 1 : 3-diol in the Prins reaction is briefly discussed.

It was shown in Part I (*J.*, 1944, 296) that propylene reacts with formaldehyde and acetic–sulphuric acids under the conditions of the Prins reaction to give three products: two of these, the cyclic formal (I; R = Me, R′ = H) and the diacetate (II; R = Me, R′ = H) of butane-1 : 3-diol, are produced by acid-catalysed addition to the olefinic double bond, but the third, 4-acetoxytetrahydro-γ-pyran (III; R = H) involves the direct reaction of the α-methylenic hydrogen activated by the hyperconjugation H—C—C=C.

The investigation has now been extended to include the corresponding reaction with the

olefins ethylene and α-methylstyrene. In the former such hyperconjugation is structurally impossible, whilst in the latter it might be expected to be greatly diminished owing to the

(I.)  CRR'(OAc)·CH_2·CH_2·OAc (II.)

relative importance of structures of the type +  in the resonance hybrid of the compound. On the other hand, polarisation of the olefinic double bond,  , in the aromatic olefin should be enhanced, and its activity thus increased. With these two olefins the Prins reaction is much less clear cut, and the products less well defined, than with propylene. Under conditions (Part I) in which propylene was rapidly absorbed and the reaction with trioxymethylene proceeded to completion, ethylene is absorbed very slowly, and reaction with the formaldehyde is very incomplete. Raising the reaction temperature to *ca.* 80°, replacement of 100% by 113% sulphuric acid, illumination, addition of mercuric salts, boron trifluoride, platinum black, or benzoyl peroxide, were all without effect in increasing the speed of absorption. A small amount of crude reaction product (23 g.) was obtained by bubbling ethylene, under slight pressure, for several days into the trioxymethylene–100% acetic–sulphuric acid reaction mixture maintained at 60—70°. Repeated fractional distillation of the crude product gave, in addition to a large number of intermediate fractions, three distinct fractions: (1) b. p. 66°/20 mm., (2) b. p. 67°/1 mm. and (3) b. p. 125°/0·8 mm. Fraction (1) is methylene diacetate obtained by simple reaction between the formaldehyde and acetic acid. Fraction (2) is essentially trimethylene glycol diacetate (II; R = R′ = H) since it is hydrolysed by 2N-sodium hydroxide to sodium acetate and trimethylene glycol, characterised as its di-*p*-nitrobenzoate, m. p. 119°. The diacetate, although analysing correctly, is, however, contaminated with about 1·8% of formaldehyde, or some product which gives formaldehyde by hydrolysis with a saturated solution of 2 : 4-dinitrophenylhydrazine in 2N-hydrochloric acid. Separation from this impurity was not possible with the quantities available. It is possible that the contaminant may be the cyclic formal (I; R = R′ = H) since, although no pure fraction of this composition was isolated, analogy with the propylene reaction suggests that it is a likely product. Some support is given to this view by the observation that pure synthetic trimethylene glycol diacetate, deliberately contaminated with dissolved trioxymethylene, could be recovered free from carbonyl activity by fractional distillation.

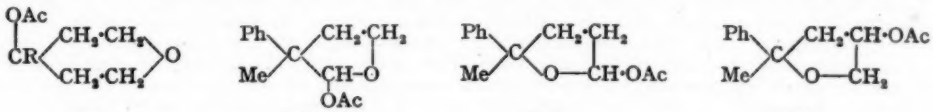
All attempts to identify fraction (3) have failed. It is an acetate and has an empirical composition almost identical with that of trimethylene glycol diacetate. Hydrolysis gives sodium acetate, corresponding to an acetyl content the same as in (2), together with a *product*, m. p. 197° (Found: C, 50·25; H, 9·59%). No structure of molecular complexity consistent with its relatively high boiling point, its analyses, and the composition of its hydrolysis product has yet been devised. Like fraction (2) it is also contaminated with about 1·2% of a formaldehyde product. Such contaminations are not surprising in view of the large excess of trioxymethylene present, owing to the very incomplete nature of the reaction.

Thus, as expected, the reactivity of ethylene is much lower than that of propylene, and the only identified product is that which arises from an acid-catalysed addition to the double bond.

Rapid reaction occurs when α-methylstyrene is added dropwise to a well-stirred mixture of trioxymethylene with 100% acetic–sulphuric acids at 40°, and examination of the products showed that considerable polymerisation of the olefin had occurred. Better results were obtained at 0°, although unreacted α-methylstyrene was then recovered from the products. These were again less well defined and difficult to purify and characterise. After isolation of the 40° reaction products in the usual manner, a small amount of a crystalline *substance* (A), m. p. 202°, of composition $C_{13}H_{16}O_3$, separated out. This product was not isolated from the products of reaction at 0°, repeated fractional distillation of which gave the following fractions: unchanged α-methylstyrene, b. p. 50·5°/18 mm.; a fraction, b. p. 86—88°/0·6 mm., from which the crystalline *formal*, m. p. 42°, of 3-phenylbutane-1 : 3-diol (I, R = Ph; R′ = Me) was isolated; a fraction, b. p. 125—132°/0·6 mm., which partly crystallised to yield a *substance* (B), m. p. 128°, isomeric with (A), and a fraction, b. p. 142°/0·5 mm., which is essentially the *diacetate* of 3-phenylbutane-1 : 3-diol (II; R = Ph, R′ = Me), contaminated with a small amount of a formaldehyde-containing impurity. A considerable amount of a residual viscous brown gum, probably polymeric products of the original olefin, remained in the distillation flask.

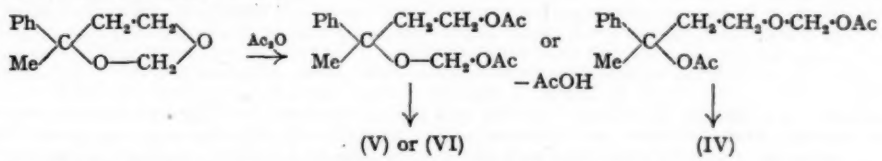
The formal is stable towards alkaline hydrolysis, but readily chars with acid hydrolysing agents. Hydrolysis with 40% sulphuric acid affords formaldehyde, characterised as its 2 : 4-dinitrophenylhydrazone, but no derivative of the corresponding diol could be isolated. The resulting unsaturated viscous gummy products suggest that the diol undergoes dehydration and polymerisation, since similar intractable products were obtained by the action of aqueous alkali on 1-*chloro*-3-*phenylbutan*-3-*ol*, synthesised by the action of methylmagnesium iodide on phenyl 2-chloroethyl ketone (Hale and Britton, *J. Amer. Chem. Soc.*, 1919, **41**, 845; cf. Kenner and Statham, *J.*, 1935, 301).

The crystalline isomerides (A) and (B) have not yet been identified. Both compounds are extremely resistant to boiling alkali, but all acid reagents, even hot concentrated hydrochloric acid, cause excessive charring with elimination of formaldehyde and the production of intractable gums. Short treatment of (B) with boiling concentrated hydrochloric acid gave a rose-red solution (suggesting a furan derivative) and a black gummy product from which a small amount of pure crystalline material, m. p. 202°, identical with (A) was isolated. Interconversion of (A) and (B) thus seems to be possible. The analysis figures for these substances agree with those required for the monoacetate (III; R = Ph), analogous to the tetrahydropyran derivative obtained in the reaction with propylene and involving α-methylenic reaction of the olefin, but the existence of *two* isomeric compounds is difficult to reconcile with this view. In an attempt to synthesis such a compound, tetrahydro-γ-pyrone (Part I, p. 300) was converted by phenylmagnesium bromide into 4-hydroxy-4-phenyltetrahydropyran, but all attempts to convert this into its acetate (even with keten) failed, the carbinol being recovered unchanged. Other possibilities for (A) and (B) are the tetrahydrofuran structures (IV)—(VI).

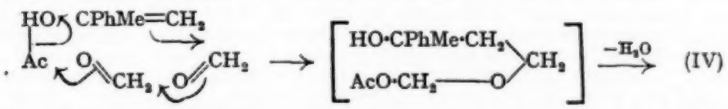


(III.) (IV.) (V.) (VI.)

These might arise by ring closure resulting from elimination of acetic acid from various acetoxymethyl ether acetates derived by the action of acetic anhydride–sulphuric acid on the cyclic formal, a reaction established for the formals of aliphatic glycols by Senkus (*J. Amer. Chem. Soc.*, 1946, **68**, 734), thus :



Alternatively (IV) might be obtained directly from the olefin by the reaction



These views would account for the existence of isomeric compounds, but the action of acetic anhydride and one drop of concentrated sulphuric acid on the pure formal, m. p. 42°, caused a vigorous exothermic reaction, much darkening, and the production of a golden-yellow gum which failed to crystallise even after being seeded with compounds (A) and (B).

In the Prins reaction, α-methylstyrene thus exhibits the expected increased reactivity in reactions which involve addition by electrophilic reagents to the double bond, whilst any reaction involving the methyl group hydrogen is very doubtful.

It is of interest to consider the structural conditions in the olefin which, in the Prins reaction, favour acid-catalysed addition to the double bond. The polarisation $CR'R''\overset{\curvearrowright}{=}CH_2$ would be expected to be an important factor. If, owing to the nature of R′ and R″, such activation is too great, the incursion of self-polymerisation side-reactions might restrict the yield of the 1 : 3-diol diacetate.

The following experimental data bear out this conclusion. In consequence of the small polarisation of the double bond, ethylene reacts very slowly and incompletely giving a very

small yield of the 1 : 3-diacetate. In propylene the increased polarisation arising from a methyl substituent, by both its inductive and hyperconjugation effects, causes facile reaction and greatly increased yield of the 1 : 3-diacetate, and similar conditions account for the ready reaction of styrene (Prins, *Chem. Weekblad*, 1918, **16**, 1510; Fourneau and Benoist, *Bull. Soc. chim.*, 1930, **47**, 860) and but-2-ene (private information kindly supplied by Messrs. Imperial Chemical Industries Ltd., Dyestuffs Division, Manchester). The accumulation of strongly electron-releasing groups at one end of the double bond will cause large polarisation, and may so activate the double bond that other condensation or polymerisation reactions may occur very readily under the conditions of the Prins reaction. In such cases, although absorption of the olefin occurs readily, the yields of the 1 : 3-diacetate are poor, and large amounts of complex high-boiling or water-soluble products result. α-Methylstyrene provides an example (this communication), and others have been observed by Messrs. Imperial Chemical Industries Ltd. (private communication), who have also observed that 2-chlorobut-2-ene undergoes the Prins reaction. In the last example the usual deactivating influence of an α-chlorine substituent towards electrophilic addition to the double bond is evidently counterbalanced by the activating polar effect of the methyl substituents. It would seem probable, therefore, that for an olefin to give satisfactory yields of the diacetate of the 1 : 3-diol in the Prins reaction the substituent groups should be of such a polar character as to ensure sufficient but not excessive polarisation of the double bond, *i.e.*, that the olefin should be of the type $CHR'{:}CH_2$ or $CHR'{:}CHR''$, where R′ = alkyl or aryl and R″ = alkyl or hydrogen.

Experimental.

Reaction with Ethylene.—Ethylene, stored in a gasometer over water, was dried by passage through phosphoric oxide and was passed under slight pressure into a mixture of 100% acetic acid (105 g.), 100% sulphuric acid (15·5 g.), and trioxymethylene (16·5 g.) maintained at 35° and shaken mechanically, using the technique previously described for propylene (Part I, *loc. cit.*). Absorption of ethylene was very slow, and neither raising the temperature to *ca.* 100° nor the other devices described in the introduction increased the absorption. The small amount of product (23 g.) investigated was obtained by slowly bubbling ethylene (14—15 l.) through a similar mixture in a flask fitted with a mechanical stirrer and heated to 65—70° for 24—30 hours, and working up the combined products of several runs in the manner described in Part I. Air was passed through the isolated crude product at room temperature to remove as much as possible of the remaining quantity of free formaldehyde. Repeated fractional distillation of the product (using the column described in Part I during the earlier stages of the distillation) gave a large number of intermediate fractions and three fractions which seemed to have constant boiling points: (1) b. p. 66°/20 mm.; (2) b. p. 67°/1 mm.; and (3) b. p. 125°/0·8 mm.

Fraction (1). The boiling point and analytical data (Found: C, 45·96; H, 6·1. Calc. for $C_5H_8O_4$: C, 45·5; H, 6·0%) show that this fraction is essentially methylene diacetate. Apart from confirmation that sodium acetate (usual tests) was produced by alkaline hydrolysis, it was not examined further.

Fraction (2). This consists essentially of trimethylene glycol diacetate (Found: C, 52·3; H, 7·7. Calc. for $C_7H_{12}O_4$: C, 52·5; H, 7·5%). The ester (2 g.) was hydrolysed with excess (15 c.c.) of 1·9N-sodium hydroxide at 40° for 15 minutes, and the homogeneous solution so obtained was exactly neutralised with dilute sulphuric acid and evaporated to dryness first on the steam-bath and then in a vacuum desiccator. The residue was extracted with boiling, dry acetone, the extract dried (K_2CO_3), and the solvent removed. The syrupy residue (0·6 g.) was converted into a di-*p*-nitrobenzoate which, after crystallisation from ether, had m. p. 119°, either alone or mixed with a genuine specimen of trimethylene glycol di-*p*-nitrobenzoate (Found: C, 54·6; H, 3·8. Calc. for $C_{17}H_{14}O_8N_2$: C, 54·6; H, 3·7%). The solid hydrolysis residue was sodium acetate (usual tests). Quantitative hydrolysis of 0·2777 g. of fraction (2) gave acetic acid equivalent to 5·84 c.c. of 0·501N-sulphuric acid, corresponding to only 1·69 acetyl groups per molecule. Corrected for the formaldehyde-containing impurity (see below), this was raised to 1·78. Hydrolysis of 0·2346 g. of fraction (2) with 20 c.c. of water and 50 c.c. of a saturated solution of 2 : 4-dinitrophenylhydrazine in 2N-hydrochloric acid gave only 0·0297 g. of a 2 : 4-dinitrophenylhydrazone corresponding to a formaldehyde content of only 1·8%.

Fraction (3). The fraction, b. p. 123—126°/0·8 mm. (Found: C, 52·5; H, 7·13%), gave the same analysis figures as did fraction (3), b. p. 125°/0·8 mm., obtained by refractionation of this run [Found: C, 52·6; H, 7·16. $(C_7H_{12}O_4)_x$ requires C, 52·5; H, 7·5%]. Quantitative alkaline hydrolysis of 0·3548 g. gave acetic acid equivalent to 7·30 c.c. of 0·501N-sulphuric acid, corresponding to an acetyl content identical with that in fraction (2). Similarly, 0·2966 g. gave only 0·0250 g. of formaldehyde 2 : 4-dinitrophenylhydrazone, representing only 1·2% of formaldehyde impurity. Hydrolysis of 0·65 g. of fraction (3) with warm 1·9N-sodium hydroxide until a homogeneous solution was obtained, and isolation of the alcohol as described above, gave a syrup which crystallised. After crystallisation from acetone–benzene this *substance* had m. p. 192° (Found: C, 50·25; H, 9·59. Calc. for $C_{15}H_{24}O_9$: C, 50·25; H, 9·57%). The presence of acetate in the hydrolysate was proved by the usual tests. No structure could be assigned to either the acetate or its hydrolysis product.

Reaction with α-Methylstyrene.—Crude α-methylstyrene (kindly supplied by courtesy of Messrs. Imperial Chemical Industries Ltd. from British Resin Products) was fractionated, using an efficient column, and the fraction, b. p. 65·5—67°/28 mm., was used. Experiments at 40° and 0° were carried out in a similar manner, and only the latter will be described. α-Methylstyrene (32·5 g.) was added dropwise over a period of 0·5 hour to a mechanically-stirred mixture of 100% acetic acid (105 g.), 100% sulphuric acid (16·5 g.), and trioxymethylene (16·5 g.), cooled at 0°. After stirring had been continued

for 0·5 hour the product was neutralised with hydrated sodium carbonate and worked up in the usual manner; yield, 53 g. of a pale yellow liquid. At a reaction temperature of 40° the product (50 g.) slowly deposited 0·5 g. of crystalline material. This, after crystallisation from methyl alcohol gave *substance* (A), m. p. 202° (decomp.) (Found: C, 70·75; H, 7·3. $C_{13}H_{14}O_2$ requires C, 71·0; H, 7·3%).

Repeated fractional distillation of the combined products gave the following fractions: (1) b. p. 50·5°/18 mm.; (2) b. p. 86—88°/0·6 mm.; (3) b. p. 125—132°/0·6 mm.; and (4) b. p. 142°/0·5 mm.

Fraction (1). The b. p., odour, and degree of unsaturation of this fraction showed that it was mainly unchanged olefin, although analysis proved it to be impure (Found: C, 87·2; H, 10·1. Calc. for C_9H_{10}: C, 91·5; H, 8·5%).

Fraction (2). This fraction partly crystallised. Crystallisation of the solid portion from ligroin (b. p. 40—60°) at 0° gave the *formal*, m. p. 42°, of 3-phenylbutane-1 : 3-diol (Found: C, 74·4; H, 7·9. $C_{11}H_{10}O_2$ requires C, 74·1; H, 7·9%).

All attempts to hydrolyse this formal with alkaline reagents (*e.g.*, boiling 4N-sodium hydroxide for 8 hours) gave only unchanged material. Acid reagents charred the formal. Hydrolysis with warm 40% sulphuric acid for a few minutes gave an odour of formaldehyde. The hydrolysate was diluted with water and extracted with ether. The aqueous liquors were partly neutralised with ammonia, buffered with sodium acetate, and treated with 2 : 4-dinitrophenylhydrazine in 2N-hydrochloric acid. The precipitated 2 : 4-dinitrophenylhydrazone, after crystallisation from alcohol, had m. p. 166° either alone or mixed with a genuine specimen of formaldehyde 2 : 4-dinitrophenylhydrazone. The ether extract contained mainly unchanged material. Longer hydrolysis with 40% sulphuric acid gave only a golden-yellow gum from which no crystalline derivative of 3-phenylbutane-1 : 3-diol could be prepared.

Attempted Synthesis of 3-Phenylbutane-1 : 3-diol.—Phenyl 2-chloroethyl ketone (8·4 g.) (Hale and Britton, *J. Amer. Chem. Soc.*, 1919, **41**, 845; cf. Kenner and Statham, *J.*, 1935, 301), cooled to 0°, was treated dropwise with the Grignard solution obtained from 1·2 g. of magnesium and 7·1 g. of methyl iodide in dry ether. The product was decomposed with ice and ammonium chloride, extracted with ether, washed, and dried (Na_2SO_4). Distillation of the residue from the dried ether extract gave *1-chloro-3-phenylbutan-3-ol*, b. p. 96°/0·5 mm. (Found: C, 65·5; H, 7·1; Cl, 20·1. $C_{10}H_{13}OCl$ requires C, 65·0; H, 7·0; Cl, 19·2%). Attempts to hydrolyse this chloride with aqueous potassium hydroxide in the cold gave similar intractable material from which no di-*p*-nitrobenzoate could be prepared. An attempt to prepare the hydroxy-ester direct from the chloride with sodium *p*-nitrobenzoate and potassium iodide at 150° (cf. Fourneau and Ramart-Lucas, *Bull. Soc. chim.*, 1920, **27**, 550) was also unsuccessful.

Fraction (3). This fraction also crystallised. After draining on porous procelain the clean solid was crystallised from ether to give *substance* (B), m. p. 128° (Found: C, 70·7; H, 7·4. $C_{13}H_{16}O_3$ requires C, 71·0; H, 7·3%). It is thus isomeric with substance (A). Substance (B) is also stable to boiling aqueous alkali, but readily chars with all acid reagents. Warming with 50% sulphuric acid gave intense charring and a pungent odour of formaldehyde. Substance (B) (0·8 g.) was boiled with 8 c.c. of concentrated hydrochloric acid under reflux for 10 minutes. The solution went pink, and black gummy material separated. The cooled solution was extracted with ether (purple aqueous layer which became turbid on dilution). The ether extracts were washed successively with sodium carbonate and water, and dried (Na_2SO_4). The black oily residue (*ca.* 0·7 g.) from the dried ether extract partly crystallised. After draining on porous porcelain the crystalline material was crystallised twice from methyl alcohol, with addition of animal charcoal, and gave substance (A), m. p. 202° (decomp.) either alone or mixed with a genuine specimen.

Fraction (4). This is essentially *3-phenylbutane-1 : 3-diacetate* (Found: C, 68·3; H, 7·4. $C_{14}H_{18}O_4$ requires C, 67·2; H, 7·2%), but it is contaminated with a little impurity which yields an odour of formaldehyde when warmed with 50% sulphuric acid. The diacetate (1—2 g.) was refluxed with alcoholic potassium hydroxide for 4—5 hours. The mixture was evaporated to dryness on the steam-bath and extracted with dry acetone. The brown viscous gum from the acetone extract was converted into a *p*-nitrobenzoate with *p*-nitrobenzoyl chloride and aqueous sodium hydroxide, warmed in the alkaline solution to dissolve any *p*-nitrobenzoic anhydride, and extracted with ether. Crystallisation from ether–ligroin (b. p. 40—60°) of the product from the ether extract gave a small quantity of material, m. p. 104°, which seemed to be an impure specimen of the *di-p-nitrobenzoate* of the 1 : 3-diol (Found: C, 63·1; H, 5·6; N, 5·6. $C_{24}H_{20}O_8N_2$ requires C, 62·1; H, 4·3; N, 6·0%). The presence of potassium acetate in the hydrolysate was proved by the usual tests.

The author wishes to thank Messrs. Imperial Chemical Industries Ltd. (Dyestuffs Division), Manchester, for assistance.

THE UNIVERSITY, LEEDS. [*Received, March 3rd*, 1947.]

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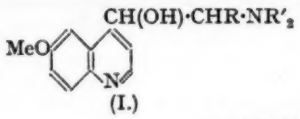
22. *Studies in the Series of 4-Substituted Quinolines.*

By J. W. CORNFORTH and (MRS.) R. H. CORNFORTH.

Some attempts to prepare analogues of quinine are described.

THE work described here was directed to the synthesis of quinine analogues of type (I; R = Me). King and Work (*J.*, 1940, 1311) have described a series of compounds in which R = H; some of these were active antimalarials. The method adopted was to condense the bromo-ketone (II; R = H) with secondary bases and to reduce the resulting keto-amines (III; R = H) catalytically. The yield in certain cases was reduced by fission of secondary amine during the reduction, with formation of the carbinol (IV; R = H).

This route was first investigated. The condensation of ethyl quininate and ethyl propionate (Rabe and Pasternack, *Ber.*, 1913, **46**, 1033) was improved and hydrolysis gave 6-methoxy-4-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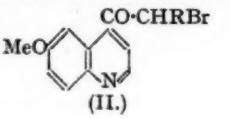
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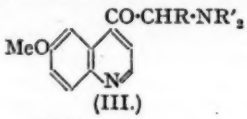
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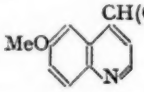
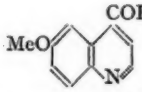
(IV.) 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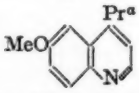
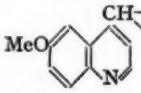
(VI.) 

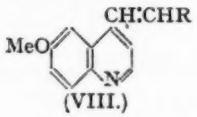

(VII.)

propionylquinoline (V). An alternative route to (V) was also examined, *6-methoxy-4-propylquinoline* (VI) being prepared from *p*-anisidine and 2-chloroethyl propyl ketone (cf. Blaise and Maire, *Bull. Soc. chim.*, 1908, **3**, 658; Kenner and Statham, *Ber.*, 1936, **69**, 16). Oxidation of (VI) with selenium dioxide, or condensation with benzaldehyde or chloral, gave no result.

Bromination of the ketone (V) gave the *hydrobromide* of (II; R = Me), and this was condensed with various secondary amines. The yield was diminished by side reactions, and the products (III; R = Me) were best isolated as their dipicrolonates. The ketone-bases (III; R = Me) were reduced under a variety of conditions. Only in the case of the piperidyl compound could the desired product be obtained, namely *6-methoxy-4-(1-hydroxy-2-N-piperidylpropyl)quinoline* (I; R = Me, NR'_2 = *N*-piperidyl). In the other cases tried, *e.g.*, di-*n*-butylamine, complete fission occurred, with production of either the ketone (V) or *6-methoxy-4-quinolylethylcarbinol* (IV; R = Me), according to conditions; on one occasion the propylquinoline (VI) was isolated. The problems presented by this stage were still unsolved when the work had to be abandoned.

iso*Nitroso-6-methoxy-4-quinolyl ethyl ketone* was also prepared; reduction with stannous chloride gave the carbinol (IV; R = Me) with fission of ammonia.

If 6-methoxy-4-(1 : 2-epoxypropyl)quinoline (VII) could be prepared, it might prove a useful source of substances of type (I; R = Me). Attempts were made to prepare this oxide from 4-propenyl-6-methoxyquinoline (VIII; R = Me), which was isolated as the *picrate* from the condensation of 6-methoxylepidine with acetaldehyde in the presence of a little acetic acid. However, no useful product could be obtained from the oxidation of (VIII, R = Me) with perbenzoic acid. The oxidation of 6-methoxylepidine and of 6-methoxy-4-styrylquinoline with perbenzoic acid was examined; *6-methoxylepidine N-oxide* and *6-methoxy-4-styrylquinoline N-oxide* were obtained. In the case of the styryl-quinoline more than one molecular proportion of perbenzoic acid was consumed, but the *CN*-dioxide was either not formed or else too unstable to be isolated. It was found that these *N*-oxides are more resistant to reduction than the oxides of aliphatic tertiary amines; *e.g.*, reduction was not effected by sulphur dioxide. This observation makes it probable that the "quinine *CN*-dioxide" of C. H. Boehringer Söhne (D.R.-P. 497,098; *Chem. Zentr.*, 1930, II, 584) is in effect the *NN*-dioxide, and the "*C*-monoxide" the *N*-oxide of the quinoline nitrogen, for it was apparently concluded that the second oxygen atom could not be attached to nitrogen because of its stability to sulphur dioxide. The properties of the monoxide (sensitivity to light, tendency to solvation) also suggest an *N*-oxide.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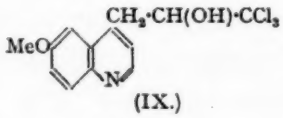
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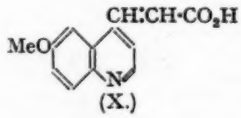
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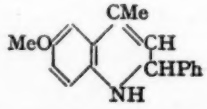
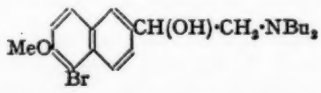
(XI.) 


(XII.)

The preparation of 6-methoxy-4-vinylquinoline (VIII; R = H) was also undertaken. Condensation of 6-methoxylepidine with chloral gave *6-methoxy-4-(3 : 3 : 3-trichloro-2-hydroxypropyl)quinoline* (IX). This was not affected by stannous chloride in acetone; reduction with

zinc in alcohol–acetic acid gave a little 6-methoxy-4-propylquinoline (VI). Hydrolysis of (IX) with alcoholic potash gave β-6-*methoxyquinolyl*-4-*acrylic acid* (X).

Addition of hydrogen bromide to (X) followed by treatment with hot concentrated potassium carbonate solution gave a small amount of 6-methoxy-4-vinylquinoline, isolated as the *picrate*. The condensation of α-picoline with acetaldehyde by means of phenyl-lithium (Walter *et al.*, *J. Amer. Chem. Soc.*, 1941, **63**, 2771) has been reported. This was tried with 6-methoxylepidine as an alternative approach to the propenyl compound (VIII; R = Me). However, addition of phenyl-lithium took place instead of hydrogen exchange, and the product was 6-methoxy-2-phenyl-4-methylquinoline, apparently produced by disproportionation of the dihydroquinoline (XI).

A compound of the naphthalene series, 1-bromo-2-methoxy-6-(2-dibutylamino-1-hydroxyethyl)naphthalene (XII), was prepared, as the *dipicrate*, by condensation of the corresponding bromoacetylnaphthalene with dibutylamine, followed by reduction.

In the course of preparation of various secondary amines, di-*n*-amylamine was prepared (cf. King and Work, *loc. cit.*) by reduction of *benzyldi*-n-*amylamine*, which was formed along with *benzyl*-n-*amylamine* by alkylation of benzylamine with amyl bromide.

Experimental.

6-*Methoxy*-4-*propionylquinoline* (V).—Ethyl quininate (82 g.) with ethyl propionate (40 g.) and benzene (120 c.c.) were treated with sodamide (20 g.). It was unnecessary to powder the sodamide provided that the lumps were not too large. The mixture was heated under reflux for 70 hours, then worked up as described by King and Work (*loc. cit.*). The crude keto-ester was hydrolysed by heating with sulphuric acid (250 c.c. of 25%) for two hours on the steam-bath. The basic ketone, recovered by means of ether in the usual manner, was extracted with hot light petroleum (b. p. 40—60°). On evaporation of the decanted solution the ketone (36 g.) crystallised and was then sufficiently pure. In addition to ethyl quininate and quininamide, quininic acid was also recovered from the reaction mixture. The quininamide was hydrolysed and the total quininic acid esterified and united with the ethyl quininate, giving a total recovery of 30 g. The yield of ketone was thus 75%, based on unrecovered ethyl quininate.

6-*Methoxy*-4-*propylquinoline* (VI).—*p*-Anisidine (9·1 g.), hydrated stannic chloride (13 g.), and alcohol (10 c.c.) were mixed and heated on the steam-bath during the addition of propyl 2-chloroethyl ketone (5 g.) dropwise during 1½ hours. After 8 hours' refluxing the mixture was made alkaline and the ether-soluble product distilled. *p*-Anisidine (4·2 g.) was recovered. The fraction, b. p. 145—200°/10 mm. (5·2 g.), was warmed with acetic anhydride (5 c.c.) for 15 minutes. Dilute acid and ether were added. The aqueous acid solution was treated with excess of ammonia, and the base taken up in ether and again extracted with dilute acid. This second extraction was necessary to remove a small amount of *p*-acetanisidide, which is appreciably extracted by acids. The *base*, recovered in the usual way, was distilled, b. p. 194—200°/10 mm. (2·9 g.), and solidified on cooling. Crystallisation from light petroleum gave colourless prisms, m. p. 56—57° (Found: C, 77·7; H, 7·4. $C_{13}H_{15}ON$ requires C, 77·6; H, 7·5%).

In one experiment when the base was liberated with sodium carbonate, crystals separated and were collected and recrystallised twice from methanol to give colourless prisms, m. p. 97°, apparently of a *carbonate* [Found: C, 68·4; H, 7·1; N, 6·0. $(C_{13}H_{15}ON)_2,H_2CO_3$ requires C, 69·0; H, 7·1; N, 6·2%]. The *picrate* crystallised from acetone in yellow prismatic needles, m. p. 196—197° (Found: N, 13·0. $C_{13}H_{15}ON,C_6H_3O_7N_3$ requires N, 13·0%).

6-*Methoxy*-4-(α-*bromopropionyl*)*quinoline Hydrobromide*.—The ketone was dissolved in hydrobromic acid (24%) and brominated by addition of the calculated quantity of bromine, either carried by a stream of air or dissolved in hydrobromic acid. The crystalline *hydrobromide* separated slowly; 39 g. were obtained from 24 g. of ketone. Crystallisation from acetone gave pale yellow prisms, m. p. 192—193° (decomp.). Analysis indicated some loss of hydrogen bromide on drying (Found: C, 42·5; H, 3·5; N, 4·0; Br, 38·0. $C_{13}H_{12}O_2NBr,HBr$ requires C, 41·6; H, 3·5; N, 3·7; Br, 42·3%).

6-*Methoxy*-4-(α-N-*piperidylpropionyl*)*quinoline Dipicrolonate*.—The hydrobromide of (II; R = Me) (1·9 g.) was added to piperidine (1·25 g.) in dry ether (5 c.c.). After one hour the piperidine hydrobromide (1·4 g.) was collected. The filtrate was washed well with water, and the ether removed at low pressure. The residue was dissolved in dry acetone (100 c.c.) containing picrolonic acid (2·8 g.). An orange-red crystalline solid separated rapidly (2·7 g.). Recrystallised from much acetone, it formed needles, which decomposed about 160—170° according to the rate of heating (Found: C, 55·4; H, 4·7; N, 16·0. $C_{18}H_{22}O_2N_2,2C_{10}H_8O_5N_4$ requires C, 55·2; H, 4·6; N, 17·0. $C_{18}H_{22}O_2N_2,2C_{10}H_8O_5N_4,C_3H_6O$ requires C, 55·65; H, 5·0; N, 15·8%).

6-*Methoxy*-4-(1-*hydroxy*-2-N-*piperidylpropyl*)*quinoline*.—The above dipicrolonate (2·7 g.) was ground with hydrochloric acid (10 c.c. of 5N), and the picrolonic acid collected and washed with more acid (15 c.c. of 5N). The base was recovered from the filtrate by means of alkali and ether, all heating being avoided; it was dissolved in hydrochloric acid (50 c.c. of N) and hydrogenated at room temperature and pressure in the presence of platinum oxide (25 mg.). The reduction was interrupted when 1 mol. of hydrogen had been taken up. The basic product was recovered as usual and treated with picrolonic acid (1·6 g.) in acetone (50 c.c.). A yellow, sparingly soluble picrolonate soon separated (1·8 g.). It was decomposed with 5N-hydrochloric acid as above. Isolated in the usual way, the *base* soon crystallised. Recrystallisation from ether gave stout colourless prisms, m. p. 118—119° (Found: C, 72·2; H, 7·8; N, 9·2. $C_{18}H_{24}O_2N_2$ requires C, 72·0; H, 8·0; N, 9·3%). The dihydrochloride formed colourless needles from acetone–alcohol, m. p. 137—138° (decomp.). On a larger scale, isolation of the product

through the picrolonate was omitted. From 7·8 g. of hydrobromide were obtained 1·35 g. of carbinol base.

Experiments with Dibutylamine.—The bromo-ketone hydrobromide (5 g.) was added to dibutylamine (5·5 g.; freshly distilled, b. p. 159—160°) in dry acetone (10 c.c.). After one hour at room temperature and 45 minutes at 45°, the solution was diluted with dry ether, the dibutylamine hydrobromide (5 g.) collected, the filtrate evaporated at low pressure, and the residue washed well with water. Addition of picrolonic acid (7·4 g.) in acetone now gave the orange dipicrolonate (6·8 g.) of the keto-base. This could not be recrystallised owing to its insolubility and sensitivity to heat. The free keto-base was prepared from the picrolonate in the manner already described; the base was used in the following reductions.

(1) Catalytic reduction in acid solution gave the ketone (V), isolated as the *picrate*, yellow needles, m. p. 174—175°, from acetone (Found: C, 51·7; H, 3·8. $C_{12}H_{12}O_2N,C_6H_3O_7N_3$ requires C, 51·4; H, 3·6%). Reduction over platinum in the presence of ferrous sulphate gave, in acid or neutral solution, *6-methoxy-4-quinolylethylcarbinol* (IV; R = Me), which crystallised in small compact prisms, m. p. 102°, from a little benzene (Found: C, 72·0; H, 7·1. $C_{12}H_{15}O_2N$ requires C, 71·9; H, 6·9%); *hydrochloride*, colourless prisms from methanol, m. p. 224° (decomp.) (Found: N, 5·7. $C_{12}H_{15}O_2N,HCl$ requires N, 5·5%); *picrate*, deep yellow prismatic needles from acetone, m. p. 178° (Found: N, 12·6. $C_{12}H_{15}O_2N,C_6H_3O_7N_3$ requires N, 12·6%). Fractionation by the method of differing basicities was generally used to examine the products.

(2) Reduction with zinc dust in cold acetic acid gave the carbinol (IV; R = Me), isolated through the picrolonate.

(3) Reduction with aluminium amalgam in faintly acid solution gave (through the picrolonate), 6-methoxy-4-propylquinoline, m. p. and mixed m. p. 57—58°.

(4) Reduction with sodium amalgam in weakly acid solution gave the ketone (V), isolated in good yield as the picrate.

(5) Reduction with aluminium *iso*propoxide in *iso*propanol gave an intractable product.

iso*Nitroso-6-methoxy-4-quinolyl Ethyl Ketone.*—Sodium (0·35 g.) was dissolved in alcohol (8 c.c.). Methoxy-4-propionylquinoline (3·15 g.), mixed with freshly distilled *iso*amyl nitrite (1·8 g.), was added gradually. After two days at 0° water and ether were added. The aqueous solution was treated with acetic acid (4·5 c.c. of 20%). The gelatinous solid was collected and dissolved in hot alcohol (300 c.c.). On cooling, felted needles (2 g.) were deposited. After another crystallisation the iso*nitroso*-derivative had m. p. 228° (Found: after drying at 100°: C, 63·7; H, 4·8. $C_{12}H_{12}O_3N_2$ requires C, 63·9; H, 4·9%). Reduction with stannous chloride in hydrochloric acid gave the carbinol (IV; R = Me), isolated as the hydrochloride.

6-Methoxy-4-propenylquinoline (VIII; R = Me).—6-Methoxylepidine (11·5 g.) with acetaldehyde (12 c.c.; pure), quinol (50 mg.), and acetic acid (5 drops) were heated in a sealed tube at 200° for 14 hours. The product was treated with ether, and the clarified ethereal solution extracted with N-hydrochloric acid. The bases were recovered in the usual way and fractionally distilled. Methoxylepidine (6 g.) was recovered; the fraction (3·8 g.), b. p. 112—135°/0·25 mm., was dissolved in hot acetone (150 c.c.) and treated with a solution of picric acid (5 g.) in boiling acetone (100 c.c.). After half an hour the product was collected and recrystallised from acetone (about 1300 c.c.). Long yellow needles (5·35 g.) of the *picrate* of (VIII; R = Me) were thus obtained, m. p. 211—212° (decomp.) (Found: C, 53·3; H, 3·75. $C_{12}H_{13}ON,C_6H_3O_7N_3$ requires C, 53·3; H, 3·75%). The free base was an oil, b. p. 118—124°/0·25 mm. During this work the picrate of 6-methoxylepidine was prepared and found to have m. p. 232—233° (Pictet and Misner, *Ber.*, 1912, **45**, 1802, gave m. p. 223°).

6-Methoxylepidine N-Oxide.—6-Methoxylepidine (3·46 g.) in ethyl acetate (12 c.c.) was treated at − 5° with a solution (73 c.c.) of perbenzoic acid in ethyl acetate (14·6 g. in 350 c.c.). After 20 hours at 0° the crystalline *oxide benzoate* was collected (2·7 g.) and recrystallised from ethyl acetate; m. p. 127—128° (Found: C, 69·2; H, 5·4. $C_{11}H_{11}O_3N,C_7H_6O_2$ requires C, 69·4; H, 5·5%). On treatment with aqueous alkali the *oxide* separated; it was recovered with chloroform and crystallised from benzene, giving colourless needles, apparently hydrated, which subsided at 151—152° and became clear at 156—157° (Found: after drying at 60°: N, 7·5. $C_{11}H_{11}O_2N$ requires N, 7·4%). The *picrate* crystallised from alcohol in long yellow needles, m. p. 171—172° (Found: C, 49·0; H, 3·7. $C_{11}H_{11}O_3N,C_6H_3O_7N_3$ requires C, 48·8; H, 3·4%). The oxide was not reduced by sulphur dioxide in chloroform, or by hydrogen in the presence of palladised strontium carbonate, but gave methoxylepidine when kept overnight with zinc dust and acetic acid.

Oxidation of 6-Methoxy-4-styrylquinoline.—The base (0·9 g.) in chloroform (100 c.c.) was treated with a solution (25 c.c.) of perbenzoic acid in chloroform (15·7 g. in 300 c.c.). After 3 days at 0° oxidation was complete. The chloroform was washed with alkali, dried, and evaporated, and the residue crystallised from a little benzene, leaving the N-*oxide* in yellow crystals, m. p. 160—162° (Found: C, 77·5; H, 5·2. $C_{18}H_{15}O_2N$ requires C, 78·0; H, 5·4%). The *picrate* crystallised from ethyl acetate; m. p. 211° (Found: C, 57·4; H, 3·9; N, 11·4. $C_{18}H_{15}O_2N,C_6H_3O_7N_3$ requires C, 56·9; H, 3·6; N, 11·1%).

Condensation of 6-Methoxylepidine with Chloral.—6-Methoxylepidine (27 g.), anhydrous chloral (27 g.), and dry pyridine (60 c.c.) were heated on the steam-bath for 7 hours. The mixture was poured into water, the solid collected, washed with alcohol, boiled with a little alcohol, cooled, collected and dried at 100° (34·2 g.). Recrystallisation from ethyl acetate gave *6-methoxy-4-(3 : 3 : 3-trichloro-2-hydroxypropyl)quinoline* (IX) in colourless needles, m. p. 195—196° (Found: C, 48·8; H, 4·1. $C_{12}H_{14}O_2NCl_3$ requires C, 48·4; H, 4·3%).

β-6-Methoxy-4-quinolylacrylic Acid (X).—The chloral compound (12 g.) was added to a boiling solution of potassium hydroxide (10·5 g.) in alcohol (50 c.c.) during ½ hour. After a further 2 hours' refluxing, water was added, and after treatment with charcoal the *acid* (X) was precipitated by acetic acid, collected, and dried (6·2 g.). Crystallisation from butanol gave pale yellow microscopic rods, m. p. 270° (decomp.) (Found: N, 6·1. $C_{13}H_{11}O_3N$ requires N, 5·8%).

6-Methoxy-4-vinylquinoline Picrate.—The acrylic acid (5 g.) in acetic acid–hydrobromic acid (30 c.c., saturated) was cooled to 0° and saturated with hydrogen bromide. After 2 days the mixture was

evaporated at low pressure. The residual crystalline cake, consisting essentially of the bromopropionic acid hydrobromide, was triturated with a little water, and the resulting suspension added gradually to a large excess of boiling saturated potassium carbonate solution covered with xylene. The mixture was boiled for an hour with one change of xylene. The united xylene extracts were washed with water, and the bases extracted with dilute sulphuric acid and passed into ether. The oil remaining after evaporation of the ether was converted into the *picrate* of (VIII; R = H), which crystallised from acetone in six-sided prisms or long needles, m. p. 210° (Found: C, 51·8; H, 3·4; N, 13·5. $C_{12}H_{11}ON,C_6H_3O_7N_3$ requires C, 52·2; H, 3·4; N, 13·5%). The yield was poor.

Attempted Reaction of 6-Methoxylepidine with Acetaldehyde.—Lithium (1·72 g.) was cut up and stirred under nitrogen with ether (130 c.c.) during the addition of bromobenzene (20 g.). Next day 6-methoxylepidine (21·6 g.; freshly distilled) in ether was added, and then a solution of pure acetaldehyde in ether, until the red colour was discharged. After 20 minutes water (25 c.c.) and then hydrochloric acid (25 c.c.; *d* 1·19) were added, and the nitrogen stream stopped. The solid was collected, stirred with sodium carbonate solution, and extracted with chloroform; the chloroform solution was united with the ethereal filtrate. On removal of solvent the residue (27 g.) largely crystallised. Recrystallisation from light petroleum (b. p. 60—80°; charcoal) gave 6-methoxy-2-phenyl-4-methylquinoline in long colourless needles, m. p. 128° (John and Noziczka, *J. pr. Chem.*, 1925, **111**, 65, gave m. p. 129°) (Found: C, 82·1; H, 6·3. Calc. for $C_{17}H_{15}ON$: C, 81·9; H, 6·0%).

1-Bromo-2-methoxy-6-(2-dibutylamino-1-hydroxyethyl)naphthalene Dipicrate.—1-Bromo-2-methoxy-6-bromoacetylnaphthalene (7·16 g.; m. p. 127—130°) in dry ether (40 c.c.) was treated with dibutylamine (5·16 g.), and the mixture refluxed for 5 hours. The dibutylamine hydrobromide was removed, and the filtrate evaporated. The residue was reduced in the known manner with aluminium *iso*propoxide in *iso*propanol (35 c.c. of 3N); reduction was complete in 2 hours. The product was converted into the picrate, which gave after three crystallisations from alcohol orange rosettes (2·3 g.), yellow when powdered, of the *dipicrate* of (XII), m. p. 147—148° (Found: C, 45·6; H, 4·0; N, 10·9. $C_{21}H_{30}O_2NBr,2C_6H_3O_7N_3$ requires C, 45·7; H, 4·2; N, 11·4%).

Benzyl-n-amylamine and -di-n-amylamine.—Benzylamine (35·7 g.), *n*-amyl bromide (100 g.), and potassium hydroxide pellets (44 g.) were refluxed (bath 150°) for 10 hours. After cooling, water was added, and the oily layer dried over potassium hydroxide and potassium carbonate, and fractionated repeatedly at low pressure, giving (1) *benzyl-n-amylamine* (6 g.), b. p. 122—124°/10 mm. (Found: C, 81·5; H, 11·0; N, 7·8. $C_{12}H_{19}N$ requires C, 81·4; H, 10·7; N, 7·9%), *hydrochloride*, needles from acetone, m. p. 240° (Found: N, 6·8. $C_{12}H_{19}N,HCl$ requires N, 6·6%); and (2) *benzyldi-n-amylamine* (40·7 g.), b. p. 151—152°/10 mm. (Found: C, 82·8; H, 11·8; N, 5·5. $C_{17}H_{29}N$ requires C, 82·6; H, 11·7; N, 5·7%).

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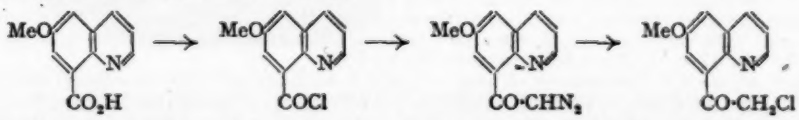
23. *Contributions to the Chemistry of Synthetic Antimalarials. Part V. Attempted Synthesis of 6-Methoxy-8-quinolyl-α-dialkylaminomethylcarbinols.*

By A. MCCOUBREY and W. WEBSTER.

6-Methoxy-8-quinolyl chloromethyl ketone has been synthesised and converted into 6-methoxy-8-quinolyl diethylaminomethyl and dibutylaminomethyl ketone. The reduction product of the former ketone has been characterised as the *styphnate*.

THE appearance of the publication entitled " α-Dialkylaminomethyl-8-quinoline methanols " by Campbell, Kerwin, LaForge, and Campbell (*J. Amer. Chem. Soc.*, 1946, **68**, 1844) prompts us to place on record our results obtained in an attempted synthesis of 6-methoxy-8-quinolyl-α-dialkylaminomethylcarbinols.

Much of our unsuccessful experimental work accords with the experience of the American workers, though we have successfully carried out (albeit in poor yield) the following synthesis of 6-methoxy-8-quinolyl chloromethyl ketone.



8-Cyano-6-methoxyquinoline (Rubtzow, *J. Gen. Chem. Russia*, 1939, **9**, 1493) was readily hydrolysed to the corresponding carboxylic acid (Rubtzow, *loc. cit.*) by boiling 60% sulphuric acid. This acid, as noted by Campbell *et al.*, was very difficult to esterify, and Rubtzow's method (heating with ethyl sulphate in alkaline solution) could not be repeated. In agreement

with the American workers, however, it was found that, of several methods tried, treatment of the acid chloride with ethyl alcohol gave the best results.

Condensation of ethyl 6-methoxyquinoline-8-carboxylate with ethyl acetate gave ethyl 6-methoxy-8-quinolylacetate which was characterised as the *picrate* and *sulphate*. Bromination of this keto-ester in chloroform or 24% hydrobromic acid led to polybrominated products as found by the American workers.

6-Methoxy-8-quinolyl methyl ketone gave, on treatment with bromine, one of two products depending on the solvent used. In chloroform a nuclear brominated product was obtained, since oxidation yielded an acidic material containing 27·8% of bromine, probably a bromoquinoline-8-carboxylic acid, though this was not investigated further. Bromination in sulphuric acid apparently led to the same polybromo-product as was obtained from the keto-ester.

Campbell *et al.* reported unsuccessful attempts to prepare 6-methoxy-8-quinolyl halogenomethyl ketones by reaction of 6-methoxyquinoline-8-carboxyl chloride with diazomethane and hydrogen chloride or bromide. In our hands 6-methoxyquinoline-8-carboxyl chloride was converted into the diazoketone which with hydrogen chloride yielded *6-methoxy-8-quinolyl chloromethyl ketone*. We found that reaction of the acid chloride in ethereal solution with a large excess of diazomethane below 0° gave the solid diazo-ketone which was stable at 0°, but decomposed rapidly at room temperature with evolution of gas and formation of an oil. The diazo-ketone was more stable in ethereal solution. If the reaction were carried out in ether above 5°, a different product was isolated, possibly 6-methoxy-8-quinolylmethyl hydroxymethyl ketone (cf. Meerwein and Hinz, *Annalen*, 1931, **484**, 1). Attempts to prepare the corresponding bromomethyl ketone led to formation of tars.

6-Methoxy-8-quinolyl chloromethyl ketone reacted normally with diethylamine and dibutylamine to give the corresponding dialkylamino-ketones. The diethyl derivative was reduced catalytically in alcoholic solution in presence of platinum oxide, reduction being terminated when 1 mol. of hydrogen had been absorbed. The dark red oil so obtained could not be distilled without decomposition, but was characterised as the *styphnate*. In view of the unpromising biological results and the difficulties of synthesis, this line of research was not followed further.

Experimental.

Ethyl 6-Methoxy-8-quinolylacetate.—A stirred mixture of sodamide (0·5 g.), ethyl 6-methoxyquinoline-8-carboxylate (2·3 g.), and ethyl acetate (0·9 g.) in benzene (6 c.c.) was heated to 90° for 3 hours. After cooling and addition of ether, the semi-solid mass was filtered off and the residue decomposed in presence of ether with 2N-acetic acid. 6-Methoxyquinoline-8-carboxylic acid (0·6 g.) was removed by filtration, and the ethereal filtrate after drying over potassium carbonate yielded a yellow oil (2·4 g.) which gave a *picrate* crystallising from alcohol in rhombs or hair-like crystals (2·55 g.), m. p. 122° (Found: N, 11·0. $C_{15}H_{15}O_4N,C_6H_3O_7N_3$ requires N, 11·1%). The *sulphate*, prepared by dissolving the keto-ester in methyl alcohol–sulphuric acid at − 70°, crystallised from alcohol in colourless crystals, m. p. 140° (decomp.) after darkening at 134° (Found: C, 48·0; H, 4·2; N, 4·0. $C_{15}H_{15}O_4N,H_2SO_4$ requires C, 48·5; H, 4·2; N, 3·8%).

Bromination of 6-Methoxy-8-quinolyl Methyl Ketone.—(*a*) A solution of the ketone (1·2 g.) in chloroform (20 c.c.) was treated gradually with bromine (0·3 g.) in chloroform (8 c.c.). The mixture was then heated to 50° for 1 hour, cooled, and filtered. The residue (1 g.) crystallised from alcohol in yellow needles, m. p. 98° followed by solidification and m. p. 150° (Found: Br, 52·0. $C_{12}H_{10}O_2NBr,2HBr$ requires Br, 54·0%).

Evaporation of the chloroform filtrate from the bromination gave a residue (0·9 g.), m. p. 166° after crystallisation from alcohol. The same *substance* was also obtained by treating the product, m. p. 98°, with 2N-sodium hydroxide (Found: Br, 28·6. $C_{12}H_{10}O_2NBr$ requires Br, 29·1%).

Oxidation of the above substance, m. p. 166° (0·4 g.), with potassium permanganate (0·5 g.) and 2N-sodium hydroxide (20 c.c.) at 100° for 6 hours yielded an acidic *substance* which crystallised from aqueous acetone in colourless plates, m. p. 220° (Found: Br, 27·8. $C_{11}H_8O_3NBr$ requires Br, 28·4%).

(*b*) A solution of the ketone (0·8 g.) in sulphuric acid (*d* 1·84; 2·5 c.c.) was treated gradually with bromine (0·65 g.). After 30 minutes, evolution of hydrogen bromide had almost ceased, and addition of ether (20 c.c.) precipitated an oil which was washed with ether. This oil crystallised when treated with a little ice, and the solid (1·15 g.) was dissolved in water and the solution basified. The resulting oil was extracted with light petroleum (b. p. 80—100°) and yielded a colourless crystalline solid (0·6 g.), m. p. 91° (Found: Br, 41·8. $C_{12}H_9O_2NBr_2$ requires Br, 41·0%).

6-Methoxy-8-quinolyl Chloromethyl Ketone.—Crude 6-methoxyquinoline-8-carboxyl chloride hydrochloride (prepared from 20 g. of acid) was added slowly during 1 hour to a stirred solution of diazomethane [from nitrosomethylurea (40 g.)] in anhydrous ether (500 c.c.) at − 5°. After 0·5 hour the mixture was filtered, and the residue washed well with ether. The combined ethereal solution was added slowly to stirred hydrochloric acid (*d* 1·16; 45 c.c.) at − 10°, the ether was decanted, the aqueous solution cooled at − 20° for 0·5 hour, filtered, and the yellow crystalline residue recrystallised from hydrochloric acid. Yield, 7·6 g. The filtrates were combined and evaporated over sulphuric acid in a vacuum desiccator. The residual tarry product, after draining on porcelain, was crystallised from hydrochloric acid. Yield,

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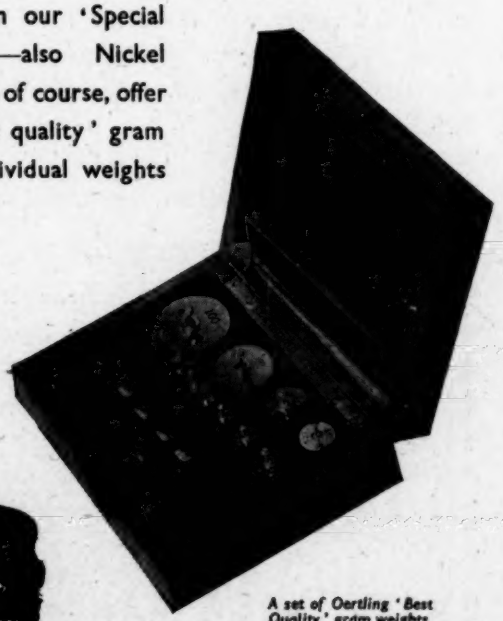

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